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The undersigned hereby certify that they have read and recommend to the School of Graduate Studies for acceptance, a thesis entitled, "A Study of Gastric Potential Difference", submitted by Arthur Jacob Oswald, B.Sc., in partial fulfilment of the requirements for the degree of Master of Science.

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A STUDY OF GASTRIC POTENTIAL DIFFERENCE

A DISSERTATION

SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

FACULTY OF ARTS AND SCIENCE

by

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INTRODUCTION

Section I.

Introduction.

A. Nature of the Problem.

Most studies on electrical potential difference of the stomach have been undertaken with the aim either of showing that electrical energy is required for the production of HCl by the stomach (23, 80) or of obtaining a clinical test for the diagnosis of gastric lesions (31, 94). In the course of these experimental attempts, numerous observations have been made which suggest that a change in electrical activity is at times secondary to circulatory changes occurring in the stomach and may not signify any primary secretory action in the glands. Such observations indicate that the vascular reactions may be a fundamental factor in the total sequence of events which normally culminate in gastric secretion.

The practical significance of this statement can be illustrated by considering the etiology of peptic ulcers. It is generally conceded that gastric acidity is a primary factor in the production of peptic ulcer. The acid appears to cause an erosion in an area of lowered resistance of the stomach (14) but here again the causative factor in producing the area of lowered resistance is purely hypothetical. Factors such as local hematogenous infection, coarse foods, food deficiencies, mucosal infection produced by embolism or thrombosis, or neurogenic causes have been suggested (13, 14, 16, 99).

Nevertheless, the production of acid and frequently hyperacidity due to overactivity of the vagus, or failure of acid inhibitory mechanisms may be the causative factor. It seems likely that circulatory derangements in the stomach may be an important primary or contributing factor in the

cause of gastric ulcer. Consequently a method of investigating gastric circulation may be of importance in assessing the significance of circulatory factors in the production or healing of peptic ulcers.

The primary aim of this investigation is to study the relationship between circulation and potential difference of the stomach, since this method of investigation might be able to add information concerning gastric vascular activity.

B. Prospective Results.

Hollander (39) in a review of the papers published on the measurement of gastric potentials finds it surprising that gastroenterologists have not been more desirous of obtaining a method of diagnosis similar to the electrocardiograph used by cardiologists. The results which have been obtained with the electrogastrograph for the diagnosis of gastric lesions (31, 94) although appearing to provide good diagnostic evidence are, however, open to considerable criticism (82). Nevertheless, Barrett (10) in reviewing recent advances in the diagnosis of gastric malignancies believes further pursuit of the problem of gastric electrical potentials might produce valuable information.

The electrogastrograph has one advantage which few gastric diagnostic techniques possess. It can make continuous recordings. This feature may bring to light information which other intermittent observations have not been able to uncover.

Another possible use for electrogastrography may be in the assessment of the vascular changes which occur in the stomach. The direct measurement of intestinal circulation in animals is difficult, and in humans is impractical. An indirect measurement of gastric circulation with an instrument such as the gastroscope is not quantitive and is open to considerable

error, since the interpretation is purely subjective. If potential changes which are induced without the stimulation of gastric secretion are a reflection of vascular changes occurring in the stomach, a new field of investigation will be opened both in clinical medicine and laboratory research.

SECTION II

REVIEW OF LITERATURE

Section II.

Review of Literature.

A. Direction of Gastric Potential Difference.

When non polarizable electrodes are placed in contact with the gastric mucosa and serosa, a potential difference exists between them in both secreting and non-secreting stomachs. In dogs, without anesthesia (70) or anesthetized with amytal (37, 71, 76, 84) or urethane and chloralose (88) the mucosa is negative to the serosa as measured in the external circuit. The same orientation of potential is found in human (31, 88), cat (93) or frog (21, 23) mucosae.

B. Origin of Gastric Potential Difference.

In the reports on electrical potentials of the stomach which had appeared before a review paper on the electrogastrograph was published by Hollander (39), potential difference was measured across the whole stomach wall. He suggested that the origin of the potential difference might be in the muscle layers. If this were the case, it would be difficult to see how the potential could be involved in the production of hydrochloric acid. Consequently, Rehm (76, 77) who was primarily interested in the possibility that electrical energy furnishes the energy required in the production of hydrochloric acid by the stomach, devised an experiment which permitted him to localize more closely the site of origin of the gastric potential. Three electrodes were used. One was placed on the mucosa, one on the serosa and the third was placed in the submusoca. Potential difference could be measured between any two of these electrodes.

Using the three electrodes, any significant potential changes which

occurred were between mucosal and serosal, and mucosal and submucosal electrodes, and not between serosal and submucosal electrodes. A drop in potential following histamine injection was recorded in the former two electrode pairs, which showed changes closely parallel to each other, but no change was recorded between the serosal and submucosal electrodes.

The direct application of alcohol (95%) to the gastric serosa, submucosa and mucosa resulted in a marked drop of potential difference only on the latter surface, which Rehm thought was some indication that potential difference arises nearer the mucosal than the serosal surface.

As a result of these observations, Rehm concluded that the E.M.F. or potential difference of the stomach originates mainly in the secretory portion of the stomach and not in the muscle layers.

C. Magnitude of the Steady State Potential.

Gastric potential records obtained when no physiological or pharmacological changes are being produced usually show a steady value of potential difference. Several authors (71, 84, 88) refer to this stable level of potential as the resting potential. This term suggests that the stomach, or at least the source of the potential, is in a state of physiological rest. Since it is very difficult or impossible to judge whether the stomach actually is at rest, an alternative term, the steady state potential, is suggested for the term, resting potential.

The steady state potential will be used in this thesis to describe the maintained potential which exists when no apparent changes in gastric potential differences are occurring. It is recognized that the steady state potential at any particular period may not therefore represent a true resting potential.

Two other arguments in favor of changing the term can also be presented. The first is that the rabbit, an animal which always utilizes its stomach for the storage of food (69) also shows a steady level of potential. But it is doubtful if the stomach in this animal can ever be in a non-digestive and non-secreting state. Secondly, it has been observed that spontaneous fluctuations in potential can occur, which are not attributable to any of the known factors which cause changes in gastric potential. New levels of potentials thus reached have also been referred to as the resting potential. For these reasons the term resting potential does not seem particularly appropriate.

Rehm (72) found an average value of the potential in non-secreting stomachs of dogs of seventy-one millivolts.

In an earlier paper (74) he rejected the use of Ag-AgCl electrodes, which were used by Rice (88), stating that considerable polarization occurred with current strengths as great as those found in the stomach. In those experiments, his prime aim was to find the maximum current which the gastric tissue could produce. Consequently a system of low resistance, non-polarizing electrodes and leads were used, which permitted greater current densities to be withdrawn than if a high resistance circuit were used. So-called non-polarizable electrodes theoretically develop a potential which remains nearly constant when the current drawn is not too great. Polarization as found by Rehm was due to changes in ionic concentrations occurring at the electrodes so that each developed a different potential. These new potentials contributed unknown values of potential difference to the gastric potential, so that a true record of gastric potential difference was not obtained. Using a high impedance electrode system, polarization does not occur readily since the current drawn is almost negligible.

When large currents are to be drawn from the tissues, those electrodes which have large surface areas will show the least polarization. By using zinc-zinc acetate electrodes with large surface areas, Crane et al (21) could maintain currents which would have polarized most silver-silver chloride electrodes.

Two electrodes are required to measure gastric potentials. Because the magnitude of the potential of each electrode is partly dependent upon the concentration of electrolyte in contact with its surface, it is imperative that the solutions at both electrodes be identical in electrogastrography. If they are not, a difference of potential (galvanic) of the electrodes will contribute to the value of the total electrical potential which is being measured.

In another series of experiments using dog gastric mucosae, Rehm (74) found steady state potentials of seventy to ninety-five millivolts with a higher average result than that obtained in his original gastrographic measurements (72). The difference was attributed to the use of a different anesthetic and to a better condition of the animals in the later work. Rice and Ross (88), also using dog gastric mucosae, recorded resting potential differences ranging between forty and one hundred millivolts.

Mislowitzer and Silver (62) recorded potentials from the gastric mucosae of cats which frequently exceeded one hundred millivolts.

Recently frog gastric mucosae have been used, since they have the advantage of maintaining a potential difference in vitro as long as aerobic conditions are present. These mucosae have potentials ranging from ten to seventy millivolts (21, 22, 64). Crane et al (23) noted a higher average steady state potential in spring than in winter.

Whether these ranges in potential difference represent species differences cannot at present be stated, since each investigator has used different experimental techniques. Another important factor which is difficult to assess is whether the stomach is really in a resting or non-secreting state at the time the measurements are made, as indicated by the following arguments.

The dog, which is known to secrete acid intermittently (5) has frequently been used as the experimental animal. When this animal has not been fed for twelve hours or so, the assumption is usually made that the secretory activity is absent and the potential recorded is a true indication of the resting stomach potential. But secretion from a fasting stomach can occur from several causes. An examination of some of these factors may partially explain why the steady state potentials quoted cover such a wide range.

Kim and Ivy (50) demonstrated that saliva and the juices of duodenal regurgitation stimulate the production of gastric juice. The period of time during which these secretions are in contact with the mucosa appears to be the only factor determining their secretogogic activity. Normally this would be very slight since they are quickly removed from an empty stomach. Rice and Ross (88) by ligaturing the esophagus and pylorus prevented stimulation by these agents, but did not prevent secretion from occurring due to salivary juices already present. Crane et al (21, 22) and Rehm (74), using washed, excised stomachs, eliminated this effect.

Insignificant particles of food residue on the mucosa stimulate gastric glands (49). This type of stimulation can be reliably ruled out only in those animals in which there had previously been a copious flow of gastric juice to wash the mucosa, or in animals in which the mucosa had been flushed clean with water or saline.

Lim, Ivy and McCarthy (55) injected 200 cc. of air into the stomach of dogs. This raised intragastric pressure about 10 mm. Hg. and provoked a slight amount of secretion. Dunn and Thompson (28) and others have shown that atmospheric air tends to come into equilibrium with blood gases in the stomach. Babkin believes the secretory effects are due to CO_2 since this gas produced secretion even when distension was avoided. In all the dogs used in the experiments herein reported, some degree of gaseous distention was found. A gastrostomy made for the purpose of introducing the intragastric lead did not always fully release enclosed gases. No note was made of distention by other investigators using intact stomachs.

It is believed that the intestinal phase of gastric secretion does not play a part in causing secretion from the empty stomach (26).. Any secretion stimulated by intestinal residue is presumably opposed to the inhibitory

effect of hydrochloric acid upon entrance into the duodenum and small intestine (1a).

It has also been shown that mechanical stimulation of the pyloric mucosa can stimulate secretion (54). It is possible therefore that in measuring electrical potentials, the intragastric electrode could stimulate secretion if it lay in contact with the pylorus. Because the potential is higher in the body and fundus than in the pylorus (61, 88), the gastric electrode is usually placed in these areas rather than in the pyloric region. Consequently pyloric stimulation is probably eliminated in experimental animals when care is taken to keep the intragastric electrode out of the pyloric region.

Conditioned reflexes which stimulate cephalic secretion (42) were probably a factor in some of the experimental reports where unanesthetized dogs were used (70). This factor would probably not be of significance in anesthetized animals, since such secretion continues for a shorter time than is required to prepare the animal for experimentation.

Ivy (42) obtained results to show that abdominal operations are likely to cause hypersecretion for days or weeks. Unfortunately he did not state how soon secretion was initiated from this cause, so this factor cannot be assessed in acute experimental procedures.

Operative manipulation also seems to affect the value of the steady state potential. The possible significance of this factor will be elaborated in Section VIa.

The effect of various anesthetics should also be considered. Chloralose and urethane were used by Babkin (6) since they do not interfere with gastric secretion. Pernoston, which has been used by Rehm in dogs, and

Mislowitzer and Silver in cats, is an anesthetic under which adequate gastric secretion is obtained (74).

After considering the numerous influences affecting the activity of an apparently resting or empty stomach, it becomes evident that many factors may still be operative in stimulating secretion. Because of the likely relationship between potential and secretion, the same factorsmay be important in determining the so-called resting potential of the stomach. There is as yet, however, little proof that many of the factors mentioned above are of great importance in electrogastrography.

D. Diffusion Potentials in Electrogastrography.

The potential set up when two solutions are in contact with each other is known as the liquid junction potential or diffusion potential (60). It is due to the unequal rates of diffusion of the ions of the two solutions into each other. The magnitude of the potential difference does not continue to increase indefinitely as diffusion proceeds, since electrostatic forces of the ions soon equalize the velocities (25). The sign of the diffusion potential between equal concentrations of two electrolytes containing a common ion may be obtained by considering the relative mobilities of the ions not shared in common. For example, at the junction between solutions of 0.1N HCl and 0.1N NaCl the salt solution will become more positive by about thirty-three millivolts (36), since the hydrogen ion has a higher rate of diffusion than the sodium ion. At the junction between unequal concentrations of similar solutions, the ions migrate more rapidly into the dilute solution. When two solutions of hydrochloric acid are considered, there is an increase in the positive electric potential in the dilute solution, due to the higher mobility of the hydrogen ion. Again electrostatic forces

prevent any analytically detectable separation of the oppositely charged ions. Temperature affects the value of the diffusion potential but only to a very small extent (37).

In electrogastrography where solutions of electrolytes come in contact with the gastric secretions, there is in all probability a diffusion potential existing between these solutions. After having considered the introductory remarks it becomes apparent that diffusion potentials can occur due to differences in ionic concentrations of the solutions and dissimilarity in mobilities of ions in the solutions.

Although it might be possible to obtain data from the literature relating to diffusion potentials between the electrolyte bathing the mucosa and the hydrochloric acid secreted in the stomach, Rehm (37) felt it advisable to determine the magnitude of these potentials under conditions more closely approximating those in which his gastric potential measurements were made. Using secreting gastric mucosae in which 0.9% sodium chloride was in contact with the mucosa and serosa, the replacement of the mucosal salt solution with 0.09% sodium chloride caused a drop in potential ranging between nineteen and twenty-three millivolts. Intermediate concentrations of sodium chloride in contact with the mucosa caused proportional decreases.

In vitro experiments using 0.9% and 0.09% saline solutions in contact with various concentrations of hydrochloric acid showed diffusion potentials quantitatively greater than the in vivo results, as illustrated in Table I.

TABLE I

Diffusion potentials occurring between solutions of varying concentration of hydrochloric acid and sodium chloride. (From Rehm, W.S., Am. J. Physiol 1947; 151,380)

	0.9% NaCl	0.09% NaCl	Increase in P.D. Between 0.9% and 0.09% NaCl
0.16N. HCl	30 mv.	61 mv.	31 mv.
0.10N. HCl	-----	------	28 mv.
0.10N. HCl & 0.06N NaCl	-----	------	25 mv.

At this time Rehm (37) felt that other factors also influenced the magnitude of the diffusion potential in vivo when 0.9% sodium chloride replaced 0.09% sodium chloride bathing the mucosa. Among these he considered undue mixing of the fluids and the occurrence of superimposed layers of electrolyte which partly accounted for the lower potential found in vivo. The layers of electrolyte which were formed by repeated replacement of the solutions in contact with the mucosa had the effect of forming intermediate concentrations of solutions and consequently the magnitude of potentials between them was not as great as if only one sharply demarkated junction was the cause of the diffusion potential. From this work his conclusion was that the decrease in potential difference across the secreting stomach is due primarily to an increase in diffusion potential and not to a change in the electrical characteristics of the stomach. In an earlier paper (74) he did not attribute all the changes in potential difference with the onset of gastric secretion to diffusion potentials.

Goodman (31) observed that the oral ingestion of milk was usually followed by an increase in the gastric potential in normal humans. Extending the work to patients with various gastric lesions, he postulated that the milk response could possibly be used as a clinical diagnostic aid. Rehm (82) found that similar results could be obtained by using a dish rather than the normal stomach. In this case the changes in potential were due to diffusion potentials only. He did not mean to imply that milk does not have an effect on gastric potentials, but that the findings of Goodman using the technique employed were unacceptable.

Crane, Davies and Longmuir (23) who used a chamber very much like Rehm for mounting frog gastric mucosae, after completing a number of experiments to determine the magnitude of diffusion potentials in their work, concluded that it seems impossible to account for potential difference changes during secretion on the basis of simple diffusion potentials. Rice and Ross (88) and Crane et al (23) found that changing the concentration of the electrolyte in contact with the mucosa and intragastric electrode did not change the recorded potential difference significantly, as long as it was sufficiently ionized to give good conductivity. Physiological saline was found to be satisfactory. Quigley et al (70) also noted that solutions hypotonic, hypertonic or isotonic with gastric secretions when placed in the stomach had no effect on gastric potentials.

Although reports to date do not unanimously conclude that diffusion potentials play only a small part, if any, in the results obtained in electrogastrography, the evidence to support the view that the potential changes associated with the onset of secretion are due only to diffusion is not conclusive either. Rehm himself in a recent publication (80) states that when 0.9% saline is in contact with both mucosal and serosal gastric membranes,

the onset of secretion is associated with a reduction of the potential difference. Only part of this decrease in potential difference he attributes to the establishment of a diffusion potential, but reserves further comment until a full report on this important problem is published. This is a more moderate view of the situation than that which he formerly held. It perhaps represents more closely the known information that diffusion potentials can materially contribute to potential changes occurring with the onset of secretion, but under most experimental conditions, diffusion potentials play only a very small part.

Other observations also suggest that diffusion potentials do not fully account for the potential changes which occur during gastric secretion. For example, gastric potential changes can occur in the stomach of a dog without any evidence of secretion taking place (88) or in the skin of a frog (57), a site from which hydrochloric acid is not secreted.

E. Secretory Activity and Potential Difference of the Stomach.

1. Introduction

In early electrogastrographic measurements, a possible relationship between secretory activity of the stomach and potential difference in gastric mucosa had been noted. However, as investigation proceeded it became apparent that there was more than one simple relationship between secretion and potential. At present the manner in which this association may be evident can be illustrated by the following statements:

1. When secretion is provoked from a non-secreting stomach, a decrease in potential occurs until a certain rate of secretion is reached.
2. Beyond the limits of secretion involved in the previous statement, further potential changes do not occur though the rate of secretion

may continue to increase. That is, during such marked secretion the voltage remains constant at a low level.

3. In a secreting stomach, agents that depress the potential difference also depress the rate of secretion or vice versa.
4. Potential changes sometimes occur without changes in secretion.

While this can be considered a valid general outline of the types of relationship existing between potential changes and secretion, some exceptions have been reported. It would appear that these exceptions can be largely explained on the basis of techniques used and on species variations. The latter factor is of particular importance. Consequently, the observations obtained from dog and frog gastric mucosae will be presented separately.

2. Comparison of Potential Changes in Dog and Frog Gastric Mucosae.

a. The relationship between gastric potentials and secretory activity of dogs.

(i) In initially non-secreting stomachs. When a stomach is stimulated to secrete, the onset of secretion is associated with a reduction of the potential difference (74, 88). Rehm (74) found that secretion induced by a single injection of histamine reached a maximum in from five to fifteen minutes and finally decreased until secretion was absent. The potential during this time showed a decrease in magnitude and a gradual return to approximately original levels with cessation of secretion. Rice and Ross (88) noted a similar relationship in stomachs that could be stimulated to secrete. However, they also observed that in some stomachs which showed no secretory response to single injections of histamine, potential changes occurred in spite of the absence of a secretory response. The magnitude of the potential difference which occurred, regardless of whether secretion was obtained or not,

was of a degree related to the dose of histamine injected.

(ii) In secreting stomachs. Rehm (74) has observed that the potential changes in response to repeated histamine injections show one major difference as compared to changes occurring due to a single injection of histamine. Repeated injections lower the steady state potential, which is usually about seventy millivolts, to about forty millivolts. However, once the minimum potential is reached, secretory activity can continue to increase still further without any further change occurring in potential difference.

Because of this finding, Rehm believes the conclusions of Quigley et al (70) are unwarranted. They found that in unanesthetized dogs, with Pavlov pouches, there was no relationship between secretion and potential. No note had been made of the secretory activity before the application of the gastric stimulants and consequently a high secretory rate could already have been present. As a result, further stimulation would not be expected to show any marked changes in potential difference of the gastric mucosa.

(iii) In secreting stomachs (in which potential difference is depressed). Solutions of hydrochloric acid varying in pH from 0.64 to 1.03, when placed in contact with a secreting gastric mucosa cause a decrease in potential as well as a decrease in secretory rate (74). In another series of experiments (75) a current passed through a secreting stomach which decreased the secretory rate also caused a drop in potential. In these experiments, the secretory rate could not be measured when hydrochloric acid was in contact with the mucosa or else the potential could not be measured when the current was being sent across the mucosa. Consequently, it was necessary to apply the experimental procedure and to measure potential and secretory changes occurring after the procedure had been employed. Thus the changes occurring in the interim could only be inferred by observations

made at the completion of each procedure. To overcome this difficulty, a technique was sought which permitted both potential and secretory measurements to be made while the potential was being depressed. The application of 0.9% saline in varying concentrations of alcohol to the mucosa was found to be effective.

Alcohol-saline solutions placed in contact with mucosa of a secreting stomach were found by Rehm (84) to depress the potential and decrease the secretory rate. The potential drop bore a direct relationship to the concentration of alcohol (3.8% to 47.5%). Following the depression of the potential difference and secretory rate, the replacement of the alcohol-saline solution with 0.9% saline resulted in a concomitant increase in both secretory rate and potential.

b. The Relationship between gastric potentials and secretory activity of frogs.

Crane et al (21, 22, 23, 24), using frogs, always found a decrease in potential associated with an increase in secretion of HCl. The magnitude of the potential change was greater for higher rates of secretion (23). The potential always increased in a secreting mucosa when there was spontaneous cessation of secretion, removal of histamine stimulation, or the addition of sodium thiocyanate which inhibited secretion. This appears to summarize the total complexity between potential difference and secretion in frogs. The relationship is a simple one, a decrease in potential with an increase in secretion, or vice versa.

3. Summary.

In review, it may be stated that the relationship between gastric potentials and secretion in frogs and dogs appears to be complex, and that

a simple statement cannot describe all the observations which have been made. At present there appear to be four main correlations between potential and secretion.

1. When secretion is provoked from a non-secreting stomach, a decrease in potential occurs until a certain rate of secretion is reached.

In frogs, the decrease in potential difference is always greater for high rates of secretion than for low rates. This appears to be the only relationship between secretion and potential difference in frogs.

2. Beyond the limits of secretion involved in the previous statement, further potential changes do not occur though the rate of secretion may continue to increase. That is, during such marked secretion, the voltage remains constant at a low level.

This dissociation of secretion and potential difference is the major difference found between dog and frog gastric mucosae. It may be significant that the maximum secretory rate in the frog (6 ml./mgm. dry wt./hr.) (23) occurs in the range of secretion in dogs in which potential and secretion bear an inverse relationship. It is only at higher rates of secretion, (the dog stomach is capable of secreting about 70 ml./mgm. dry wt./hr.) (80) that the potential does not vary with further increases in secretion. This perhaps is a result of an evolutionary process which has been more highly developed in the dog in order that it may attain high acid secretory rates for the purpose of more easily and readily digesting its food. However, the importance of this fact in interpreting results in dog gastric mucosae can only be speculative until the mechanism of secretion is more fully understood.

3. In a secreting stomach, agents that depress potential difference also depress the rate of secretion.

The mechanism by which hydrochloric acid lowers potential in a secreting stomach is obscure.

The manner in which electric currents act, however, can theoretically be attributed to its functional significance in the production of hydrochloric acid. Rehm (80) has implicated an electric current produced in some unknown manner by the gastric mucosa, as exerting a controlling influence on the secretion of hydrochloric acid. When a current is applied to the gastric mucosa in such a manner as to lower potential, it acts by opposing the inherent current of the tissue and consequently, secretion also is depressed.

The alcohol-saline solutions could possibly act by a direct narcotic effect being exerted on the parietal cells. This could lower the vital activity of the cell so that potential and secretion would be depressed.

4. Potential changes can occur without changes in secretion. Rice and Ross (88) first noticed that histamine and pilocarpine could affect potentials without causing secretory function to be altered. Whether the circulation in the stomach was in some way responsible for the anomalous occurrence or not was speculated upon. It is the aim of this thesis to obtain evidence that this is the case. Other observations also point toward implicating the vascular supply of the stomach as a factor influencing gastric potentials, but these will be presented in detail later.

F. Sources of the Changes in Gastric Potential Difference Due to Secretory Stimulation.

1. Introduction.

In the previous section, gastric secretory activity was shown to be associated with some of the changes occurring in electrical potentials.

Since gastric secretion is composed of several substances, the author thought it advantageous to find which of the different products was mainly responsible for the potential changes which were observed. To a limited extent, certain of the various components of gastric secretion can be stimulated separately. An analysis of the date obtained by this selective stimulation is undertaken with the purpose of showing that the potential changes which occur are due to the secretion of hydrochloric acid and not peptic and mucoid substances.

2. Pharmacological Secretory Action of:

a. Histamine

Gastric secretion can be induced by histamine in dogs with denervated pouches (44), transplanted pouches (43, 52), or after degeneration of the vagus nerve has occurred (48). As a result of these observations, histamine is said to act on the peripheral neuro-cellular structure and probably directly on the cellular structure itself (8). The secretion produced by histamine stimulation is predominantly hydrochloric acid. The peptic and mucoid cells which supply the juice containing enzymes and organic substances are only very slightly stimulated, if at all (51, 30). It may well be that the slight amount of peptic power found in histamine-stimulated secretion is the result of the washing out of enzymes present in the gastric tubules when hydrochloric acid secretion is stimulated by histamine (30, 2).

b. Pilocarpine.

In dogs, pilocarpine stimulates chiefly the output of pepsin and organic substances, producing hydrochloric acid to a lesser degree (44, 97). Babkin (2) also found that although the secretion from the peptic cells continued in response to prolonged pilocarpine stimulation, the secretion of hydrochloric acid returned to initial levels after about an hour.

c. Mecholyl.

Injections of mecholyl in dogs were found by Gray and Ivy (32) to increase gastric secretion, but after reaching a maximum, a decline in secretion occurred despite continued injection of the drug.

3. Electrogastrographic Changes Due to:

a. Histamine.

One injection of histamine causes an increase in gastric secretion and a decrease in electrical potential. After a short time, both potential and secretion return to approximately original values (72, 74). Repeated injections of histamine maintain a high rate of secretion and a decrease in potential of about 30% to 50% of the steady state value. A low potential is reached in approximately fifteen minutes, after which no significant potential changes occur, while the secretory rate continues to increase to a maximum which might require an hour before it is attained (74).

Mislowitzer and Silver (61), Rice and Ross (88), Sawyer et al (94) and Crane et al (23) also found a decrease in potential in response to injections of histamine.

Quigley et al (70), using unanesthetized Pavlov pouch dogs, found that histamine did not affect gastric potentials. Since they did not measure gastric secretion, it is possible that the mucosa was already actively secreting, so no further potential difference changes would be expected to occur.

Sarre (92) reported that there was an increase in potential difference when the stomach was stimulated by injections of histamine. Rehm (74) proposes a possible explanation for this apparently conflicting observation.

b. Pilocarpine.

Rehm (74) obtained a decrease in potential with an increase in secretion in three out of seven experiments in which pylocarpine hydrochloride

was used as a gastric stimulant. In these experiments the secretory rate reached a maximum and finally decreased despite repeated injections of pilocarpine. The potential curves were very similar to those obtained with histamine stimulation.

Rice and Ross (88) gave forty-five intravenous injections of pilocarpine to anesthetize dogs. They noted a fairly typical response, the magnitude and duration, however, being partly dependent on the size of dose. A drop in potential occurred which reached a maximum in two to fifteen minutes. A gradual recovery to approximately original value followed the initial drop. Sometimes a notch occurred during the drop in potential. This was also found in some of the histamine experiments (compare Figs. 5 and 8, Rice and Ross (88)) which were reported.

Quigley et al (70) reported that there was no significant change in potential following injections of pilocarpine.

c. Mecholyl (Acetyl-beta-methylcholine chloride).

Rehm (84) also used the parasympathomimetic agent, mecholyl, to stimulate secretion. It decreased potential and increased gastric secretion. The secretory rate increased to a maximum and then decreased despite continued administration of mecholyl. The potential difference in the gastric mucosa gradually rose as secretion diminished. He noted that potential difference curves obtained by this method closely resembled potential difference responses after injections of histamine.

4. Summary and Conclusions.

A summary of the observations reveals:

1. That histamine stimulates only the secretion of hydrochloric acid and the potential drops with histamine stimulation.

2. That mecholyl and pilocarpine stimulate not only hydrochlor-

ic acid but also mucoid and peptic secretion. The potential drops in response to these agents.

3. That although repeated injections of pilocarpine and mecholyl stimulate continued secretion of mucoid and peptic substances, the acid secretion becomes refractory and finally decreases. The potential after an initial drop also increases following repeated injections of these agents.

As a result of the dissociation of hydrochloric acid secretion from mucoid and peptic secretion, and the resultant changes in potential, it appears that these latter secretions do not contribute to the changes in potential during secretory activity in the stomach.

Whether they ever contribute to potential changes found in the stomach requires further investigation. Perhaps a method whereby such an investigation could be made would be in stomachs which have achlorhydria where peptic and mucoid secretion could be stimulated without the presence of hydrochloric acid.

In conclusion it can be stated that the potential changes which occur during gastric stimulation due to histamine, pilocarpine and mecholyl can be attributed only to the secretion of hydrochloric acid.

G. Other Observations on Gastric Potential Difference.

Numerous agents and procedures have been used to modify the gastric potential difference. A summary of some of these will be presented in this section. A complete account of the conditions of each experiment can be found by consulting the original paper.

Vomiting, pulmonary edema or bradycardia were found to lower the magnitude of the steady state potential (61). Respiratory movements or hunger contractions did not appear to affect the gastric potential difference of

unanesthetized pouch dogs (70).

Quigley et al (70) and Crane et al (23) concluded that the pH of solutions placed in contact with mucosa did not produce changes in potential difference. Mond (64), however, found that increasing the hydrogen ion concentration of solutions in contact with gastric mucosa resulted in a decrease in potential.

Quigley et al (70) reported that milk increased the potential in Pavlov pouch dogs. Adair and Goodman (1) in a preliminary report found either an increase or a decrease in potential, due to the oral ingestion of milk. The work of Rehm (82) and Goodman (31) on the effect of milk on gastric potential has already been reviewed on page 14.

Rice and Ross (88) found some evidence that central and peripheral vagal stimulation or section of the vagus caused a decrease in gastric potential. Mislowitzer and Silver (61) found that these procedures had little effect on potential difference. Rehm (84) was not successful in producing a change in gastric potential difference with vagal stimulation. In all these experiments, it was stated that more date is required before the evidence can be considered to be conclusive.

Mond (64) and Quigley et al (70) did not note a change in gastric potential with atropine. Non-secreting stomachs were found by Rehm (84) to be unaffected by atropine. In stomachs secreting due to pilocarpine stimulation however (84, 88), atropine was found to restore the gastric potential and to decrease the secretory rate.

Sodium fluoride, sodium cyanide, sodium thiocyanate, procaine, mercuric chloride and zinc sulphate decreased both potential and secretion in secreting stomachs (27). Crane et al (23) found that hydrogen cyanide, chloroform and iodoacetate inhibited gastric secretion, and that gastric

potential difference fell to zero in isolated frog stomachs.

Quigley et al (70) reported that dextrose in contact with the gastric mucosa resulted in an increase in potential, while Rice and Ross (88) found that twenty-five milliliters of a five percent solution of sucrose did not give any consistent or significant changes in potential. Intravenously (70), dextrose was found to be without effect on gastric potential difference.

Acetylchlorine did not appear to affect the gastric potential (64). Attempts by Rehm (84) to produce changes in gastric potential with acetylcholine were unsuccessful. Corn oil (88) in contact with the gastric mucosa did not modify gastric potential difference, while fat (70) was found to decrease gastric potential.

Rehm (83) found no change in the steady state potential of dogs following injections of 1.2 to 2.4 grams of sodium thiocyanate. In secreting stomachs, however, sodium thiocyanate inhibited secretion and increased gastric potential. The secretory and potential changes did not always occur simultaneously (81, 83).

The intravenous injection of ethyl alcohol did not alter the steady state potential of dogs (70, 84). The direct application of ethyl alcohol to the gastric mucosa decreased gastric potential in dogs (88), and in cats (84). Quigley et al (70), however, concluded that the augmentation of secretion by contact of ethyl alcohol with the gastric mucosa was not related to gastric potential changes. Rehm (84), who has investigated the effects of ethyl alcohol on gastric potentials more thoroughly than previous investigators, found that alcohol-saline solutions caused a decrease in the steady state potential without the secretion of hydrochloric acid occurring.

He also noted that alcohol-saline solutions decreased both potential and secretory rate in secreting stomachs. The effects were not found to be

due to diffusion potential. Still further investigation is required, however, before it can be said that the effects of alcohol on gastric potential are fully understood. In the first place, some of the investigators reported that there was no stimulation of secretion while it is known that alcohol is a gastric stimulant by whatever route it is administered (12). Also Osterhout (67) recommends that only low concentration of alcohol be used in contact with tissue cells (Nitella) in order that injury be prevented. The gastric mucus may, however, protect the stomach against high concentrations of alcohol. As a result, the above observations should be accepted with reservation, until the various effects of this drug on secretion, diffusion and injury are clarified.

Bajandas et al (9) could modify potential difference by changing the oxygen tension of solutions in contact with the gastric mucosa. After a decrease in potential was induced, aerated or oxygen-free saline when replaced by oxygen-saturated saline produced an increase in potential difference within about one minute. In isolated frog gastric mucosae, an adequate supply of oxygen in the fluid in contact with the mucosa is necessary to maintain acid secretion and potential difference across the membrane (21, 23).

Rehm (73) produced areas of injury on dog gastric mucosa and found that there was a decrease in potential in the injured area. The magnitude of the injury potential was approximately equal to the magnitude of the change in potential which occurred across the stomach. The injured areas were formed on intact mucosae of dogs' stomachs by the application of boiling Ringer's, ether or alcohol.

SECTION III

THE RELATIONSHIP OF VASCULAR CHANGES TO GASTRIC POTENTIAL DIFFERENCE WITH A NOTE ON THE ACTION OF ADRENALIN ON INTESTINAL CIRCULATION AND GASTRIC SECRETION

Section III.

The Relationship of Vascular Changes to Gastric Potential Difference with a note on the action of Adrenalin on Intestinal Circulation and Gastric Secretion.

In recent years considerable impetus has been given to the study of the electrophysiology of the stomach because of its possible importance in the production of hydrochloric acid. The measurement of gastric potentials has been primarily concerned with their relation to the secretory functions of the stomach, while only limited attention has been paid to their connection with circulatory phenomena.

There is good reason to believe that, as in other glandular systems, increased gastric secretion is associated with an increased gastric blood flow. Lim et al (55) states that "all stimuli that excite gastric secretion act essentially by increasing the active blood flow through the stomach". But it cannot be assumed that a change in circulation always results in a corresponding change in secretion, and in fact, the precise relationship between the secretory state of the glands and their blood supply has not been clearly defined. Crane, Davies and Longmuir (21, 22) concluded that since secretion and gastric potentials are abolished by lack of oxygen, the electrical energy of the mucosal cells is derived from cellular respiration. Further, Rice and Ross (88) described reductions of potentials under the influence of adrenalin and other conditions which apparently reduce oxygen transport to the stomach.

It appears, therefore, that changes in gastric potential may result not only from changes in the secretory activity of the gland cells, but also from circulatory adjustments in the stomach. It is important to know

the degree to which these two causes of potential change are associated or are independent, since efforts are being made to make diagnostic use of the gastric potentials. The tendency has been to attribute gastric potential changes primarily, or even exclusively, to alteration of secretory activity in the gland cells. However, much emphasis is being placed on intracellular oxidation -reduction reactions as the immediate source of the bio-electric currents (58). Normal aerobic respiratory processes are assumed to give rise to electromotively active materials, without any association with the formation of secretory products. The maintained E,M,F. consequently vary with oxygen pressure and other factors influencing the rate of metabolism (91).

Therefore, while admitting that the source of the gastric potential lies within the mucosa cells (76), the following evidence suggests a change in electrical activity is at times secondary to circulatory changes, and may not signify any primary action in the glands.

1. Adrenal reduces the gastric potential apparently through vasoconstriction (88).

2. Prolonged fall of blood pressure reduces the potential difference (61, 83).

3. Mechanical interference with blood flow by pressure or vascular occlusion lowers the potential (9, 76).

4. Potential difference across the stomach is dependent on an adequate blood supply (76).

5. Injections of large doses of sodium thiocyanate in the dog in a short period of time often resulted in a decrease in pulse rate, blood pressure and potential difference (83).

6. Reflex and emotional stimulation in animals and man reduces gastric potential; conditions which would not likely be associated with

stimulation of the gastric glands, but would likely be associated with vasomotor changes (88).

7. Anoxia decreases gastric potential difference (84).

8. Death of an animal reduces gastric potential to zero (21, 88, 94).

It is important that the influence of the circulation over the gastric potentials should be clearly defined for two reasons. First, when responses are abnormal, one must know whether they are due to abnormality in the secreting cells (e.g. defective secretory ability), or to unusual circulatory activity. Second, if a pattern of potential changes can be reliably related to circulatory activity in the stomach, the electrogastrograph might offer a means of assessing the circulatory efficiency of the stomach. It might then be of importance not only in the diagnosis of specific gastric diseases such as gastric ulcer and carcinoma, but may also provide evidence of functional disorders such as vasospasm. In the latter case, abnormalities of the gastric potential difference may indicate constitutional disorders, such as incipient hypertension, or neuro-psychiatric conditions.

This thesis deals primarily with the vascular activity in the stomach and its relationship to the gastric electric potentials. For this reason, a resume of the probable effects of various pharmacological agents on the intestinal circulation and on gastric secretion is given.

Epinephrine (adrenalin) acts as a potent pressor agent by causing peripheral vasoconstriction, increased heart rate and myocardial stimulation. Since the work of Oliver and Schafer (65), it has been credited with having a powerful vasoconstrictor effect on intestinal circulation. This evidence was substantiated by others including Hartman (33) and Erlanger and Gasser (29). Clark (18) found that this constitutes the only vascular response to small doses of adrenalin.

However, when larger doses were injected, sufficient to give a definite pressor response, there was always an initial drop in intestinal volume of short duration and a subsequent prolonged increase in volume with a relatively slow return to original volume (18, 34, 35).

The initial decrease in volume is generally attributed to splanchnic vasoconstriction caused by adrenalin.

The secondary increase in volume, however, may be the result of at least three mechanisms:

(i) Passive congestion of the portal system caused by hepatic vasoconstriction (47). They also found that portal flow in dogs at first decreased and later increased.

(ii) Reflex dilation of neurological origin resulting from the initial increase in blood pressure and mediated through a mechanism such as the carotico-aortic system (17).

(iii) A response of adrenalin on splanchnic vessels which is dilator in type (35).

It is difficult to postulate the exact mechanism involved, partly because the experimental evidence is indecisive, and partly because of species variation. For example, Bulbring and Burn (15) reported a primary decrease in volume followed by an increase and noted that the variations of volume due to adrenalin were more marked in the cat than in the dog. It is common knowledge that the rabbit also possesses a very labile vasomotor system compared to the dog, a point which may be of significance to this thesis since rabbits largely were used.

In order to rule out the possibility that the gastric potential changes which occur when adrenalin is injected are due to secretion and not purely vasomotor changes, a review of pertinent literature was undertaken.

Inhibition of gastric secretion was observed in man and dogs by Moll and Flint (63) and Rogers et al (90), but stimulation was found by Lim (53), Ivy and McIlvain (45) and Baxter (11) after injections of adrenalin. All investigators found that the secretory effects were not immediately evident and that a latent period of several minutes to half an hour occurred. It is difficult to assess this latent period in relation to the onset or inhibition of secretion, since techniques do not permit the collection of samples immediately following injection of the drug, because measureable quantities of secretion are required before determinations can be made. Babkin (7), in a review of the evidence in favor of a sympathetic secretory mechanism, points out that no conclusive decisions can be made, so it is possible that adrenalin is not a gastric secretory stimulant. If this is the case, it is also probable that the potential difference changes which occur due to adrenalin cannot be attributed to its gastric secretory effect.

There is no comparable amount of literature pertaining to the effects of the other sympathomimetic amines used in the following experiments on intestinal blood.flow. Consequently the measurement of the carotid blood pressure is the only indication that vasomotor adjustments and circulatory changes are taking place.

SECTION IV.

TECHNIQUE

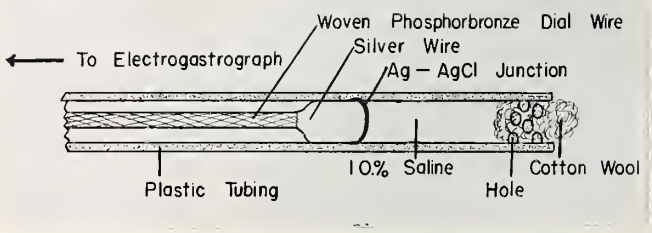

DIAGRAM II Schematic diagram of the electrogastrograph electrodes.

potential difference also was minimized by using a high impedance input system.

2. Calibrator.

The calibration circuit is shown on the left hand side of Diagram I. By turning the selector switch potentials of ten to seventy millivolts could be obtained from a voltage divider in ten millivolt steps. After the completion of each experiment, but before the gain control was reset, a record of the calibrated voltages was made so that the values of the potential difference obtained during the previous experiment could be determined.

3. Galvanometer.

The galvanometer was of d'Arsonval type using two two-inch permanent magnets of the type used in small loud speakers. The moving coil was suspended vertically by wire obtained from the recording spool of the wire recorder. The upper suspension was attached to a movable socket which permitted the galvanometer coil to be rotated manually. After having moved the electrogastrograph, vertical suspension of the coil was again obtained by aligning a plumb-bob by adjusting thumb screws attached to the wooden base of the equipment. The moving coil was wound with two thousand turns of No.42 enamel covered wire and had a D.C. resistance of 4,200 ohms.

4. Electrodes.

Two electrodes were constructed (Diagram II). One end of a one inch length of silver wire was formed into a rounded bead about two millimeters in diameter. The other end of the silver wire was soldered to a piece of woven phosphorbronze dial wire which was threaded through a thirty inch piece of flexible plastic tubing of 1.5 millimeters inside diameter. The bead on the silver wire was then pulled into the lumen of the plastic tube for a distance of about three inches. The lumen of the plastic tubing

distal to the silver bead was used in the preparation of a saline bridge. The silver bead formed a mechanical obstruction to the escape of saline into the tube containing the phosphorbronze wire which was insulated throughout its length by the plastic tubing.

Seven or eight holes were cut in the distal inch of the plastic tubing. A deposit of silver chloride was laid on the surface of the silver bead and the lumen of the tube distal to the bead filled with ten per cent saline. A plug of cotton wool moistened in saline was inserted into the tube far enough to prevent the escape of saline from the windows cut in the wall of the plastic tube. The holes in the tubing prevented the electrode from becoming occluded by end on pressure against the gastric wall. Ten per cent sodium chloride was used in the electrodes, since this concentration of electrolyte provided satisfactory conductivity (88). The phosphorbronze wires were connected to the metallic input leads of the amplifier.

One electrode was used as the intragastric lead and the other as the extragastric lead.

Before starting any recording, the electrodes were placed in a beaker of ten per cent saline. If any polarization potential greater than one or two millivolts existed between the two electrodes, the silver-silver chloride junction was replaced. Significant polarization usually occurred only after thirty or forty hours of operation. At the end of each experiment the electrodes were again placed in a beaker of ten per cent saline and any drift which had occurred due to amplifier instability was noted. When base line drift greater than two millivolts was found to have occurred, a true value of the gastric potential difference was obtained by making a correction in the calibration voltage scale.

5. Recording.

a. Potential difference.

A silvered microscope cover slip was attached to the galvanometer coil. A light beam reflected from this mirror recorded movements of the galvanometer on slow-moving, five by seven inch Velox FO paper. The paper was driven by a small electric motor at a speed which required fifty minutes to expose its full length. A time switch connected to the drive mechanism illuminated, from a separate light source, the optical slit throughout its length after every five minutes of operation. This produced the vertical lines which are shown on the electrogastrograms. Another light beam also reflected from the galvanometer mirror was focussed on a red-glass viewing screen. The voltages being recorded during an experiment could be observed on this screen.

A record of the time at which any procedures were undertaken was obtained by exposing a marginal segment of the paper from an independent light source.

b. Blood pressure.

Blood pressure records were obtained from a cannula tied in a carotid artery and attached to a mercury manometer. An arm attached to the manometer float recorded blood pressure changes on a kymograph paper which was moving at a slightly faster rate than the photographic paper used to record gastric potential difference. Half minute time intervals were recorded on the tracing. A record was also made on the blacked kymograph paper of any procedures which were undertaken. The illustrations used in this thesis show potential and blood pressure recordings which have been reduced to the same time scale.

B. Procedure.

1. Anesthesia.

All rabbits were anesthetized with urethane and ether. 1.5 grams per kilogram body weight of a twenty per cent solution of urethane was injected subcutaneously at two or three sites in the backs of the animals. An hour later sufficient ether by open drop was administered to lower and maintain the depth of anesthesia at the third or fourth plane of stage three for the remainder of the experiment. Urethane was chosen as an anesthetic agent since it has been shown (6) that it does not interfere with gastric secretion.

The dogs used in these experiments were first given a sedative dose of morphine intravenously (three milligrams per kilogram of body weight). An intravenous injection of sodium amytal (thirty milligrams per kilogram of body weight,) was given half an hour following the morphine to produce anesthesia. The amytal has been shown by Olmsted and Gerogossintz (66) to check glycogenolysis when injected later than the morphine.

2. Preparation for placement of the gastric electrodes.

Following the procedure of Rice and Ross (88), the pylorus and cardiac sphincters were ligated in the first twelve rabbits used. The abdomen was opened through a midline incision and the stomach exposed. A glass tube about fifteen centimeters long was then tied into a gastrostomy made in the anterior surface of the stomach. A 0.9% saline solution was poured into the stomach until it half filled the protruding glass tube. The intragastric electrode was inserted through the glass tube until it lay in the lumen of the stomach.

The stomachs of these first twelve rabbits were markedly distended with dry, fibrous green contents. This material formed a tough matted

ball in the lumen. It was necessary to remove a considerable amount of this material before any liquid could be poured into the stomach. 0.9% saline was used as the conducting electrolyte since it was found satisfactory by Rice and Ross (88).

In tying the pyloric sphincter, care was taken to exclude any of the larger vessels from the ligature. After these preparations, the abdomen was closed by interrupted sutures.

In the remaining twenty-seven rabbits which were used, it was decided to decrease the quantity and consistency of the gastric contents, since records of low potential difference were being recorded. This was accomplished by starving rabbits which had been fed on a commercial preparation of dried cereals and alfalfa for four or five days. A diet of fresh carrots, cabbage and oats was then substituted for the commercial feed for the next week. An abundant supply of water was always present in the cages. By means of this dietary regime, the quantity of contents was greatly reduced. The stomach now contained a semi-fluid chyme rather than a dry pulp as previously found. At the same time, it was decided to decrease manipulation and operative procedures on the stomach. Instead of being inserted through a gastrostomy, the intragastric electrode was inserted into the stomach through the esophagus. A ligature was placed around the esophagus and electrode in order to hold it in place. Sufficient semi-liquid contents were present in these animals to obtain a good contact for the electrode, so no saline was used in the stomach.

The abdomen was opened, however, for the purpose of locating the position of the electrode in the lumen and also for the purpose of inserting a tube into the stomach through which samples of gastric secretion could be obtained. This was also the method of preparation used in the dogs.

3. Method of obtaining gastric contents.

The drainage tube was a twelve inch length of plastic tubing the same as that used in the electrodes. In the distal end, a series of holes about an eighth of an inch in diameter was cut and the proximal end was fastened to an aspirator bottle. The distal end of the tube was inserted into the pyloric region of the stomach through an opening made in the duodenum. A ligature was tied around the duodenum and drainage tube to prevent it from slipping out of the stomach, and at the same time to prevent the loss of gastric contents into the duodenum. A vacuum of about thirty centimeters of water pressure was used to evacuate the fluid gastric contents.

Each time three milliliters of contents were collected in the aspirator bottle, a new bottle was substituted and the sample number marked on the kymograph tracing. The pH of the gastric contents was determined on the Beckman pH meter using a glass electrode.

4. Injections.

All injections of pharmacological agents were made intravenously. A canulla attached to a reservoir of 0.9% saline by means of a rubber tubing was tied into the femoral vein. Injections were made through the rubber tubing and a signal mark was recorded during the injection on both kymograph and electrogastrograph records. About one milliliter of saline was used to wash out the lumen of the canulla after each injection. Injections were usually started only after the steady state potential and carotid blood pressure had been maintained at a constant level for at least five minutes..

5. Preparations for taking electrogastrograms in humans.

Human subjects were requested not to eat any food for a twelve hour period prior to the taking of the test. The subject was seated comfortably and was given the intragastric electrode to swallow. If any difficulty

arose, the subject was permitted to drink about fifty milliliters of water to aid in swallowing the tube.

The lower third of the antero-lateral surface of the upper arm was rubbed with electrocardiographic electrode paste until an erythema was produced. The extragastric electrode was placed in this area and was covered by a pad of cotton gauze which had been soaked in warm 0.9% saline. The pad was held in place by a piece of rubber dental dam which was wrapped around the arm. The room in which the tests were conducted was kept at a comfortable body temperature and as free from extraneous noises as possible. The milk and water which were used in the tests were warmed to room temperature.

SECTION V

RESULTS

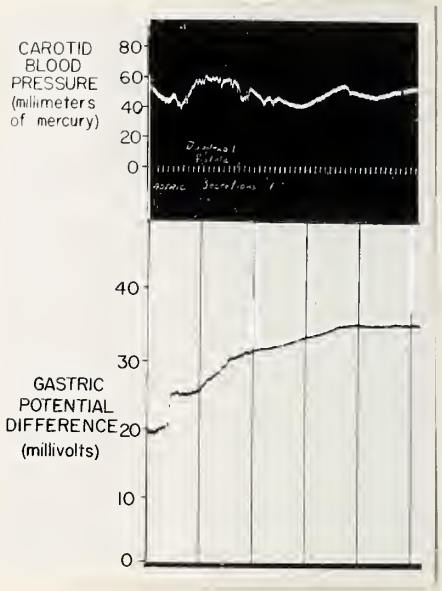

FIGURE I The increment in gastric potential difference observed following the cessation of operative manipulation. Rabbit 32.

Section V.

Results.

A. The Steady State Potential.

After completing the necessary preparation required for the measurement of the gastric potential and carotid blood pressure, it was observed that a variable length of time was required before the steady state potential was reached. The time was frequently as short as five minutes or even as long as forty-five minutes. Figure I# shows the increment in potential which occurred in Rabbit 32, and is indicative of the increase which occurred in the other rabbits also. An increase in gastric potential found at the start of the animal experiments was also frequently recorded from human subjects. An extreme example of the increase which occurred is illustrated in Figure XIX.

In the initial series of thirteen female rabbits in which esophageal and duodenal ligatures were applied, the steady state potential was never greater than forty millivolts. In six it was less than ten millivolts. In the remaining twenty-seven rabbits, the steady state potential on several occasions was as high as seventy millivolts and never less than twenty millivolts.

Similar observations were made on the steady state potentials of the eleven dogs used in these experiments. The average resting potential was fifty-six millivolts. In only one dog, in which the potential was twenty-five millivolts, was the potential difference below forty millivolts. The highest

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Simultaneous records of blood pressure and gastric potential difference are shown in Figure I and succeeding illustrations. The top record is the kymograph tracing showing carotid blood pressure, time record in half minutes, and signal marker record from above downwards. Below it is the electrogastrograph record showing the potential difference. Projections on the base line indicate physiological procedures. The vertical lines in this and succeeding electrogastrograph records represent five minute time intervals.

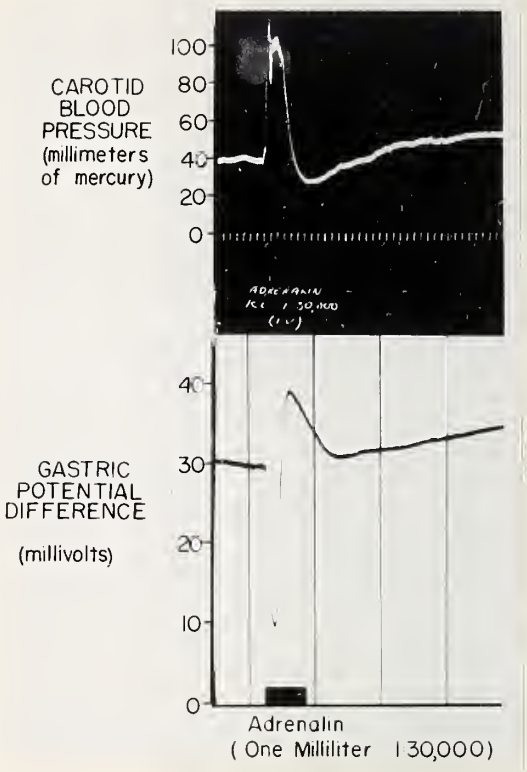

FIGURE II The effect of one milliliter 1:30,000 adrenalin (15 ug. per Kg.) on carotid blood pressure and gastric potential difference. Rabbit 32.

potential recorded was seventy-five millivolts.

The mucosa was in each case negative with respect to the serosa as measured in the external circuit. This is in accord with other observations on the orientation of the potential difference of the gastric mucosa.

B. The Effect of Sympathomimetic Agents on Gastric Potential Difference and Carotid Blood Pressure.

1. Adrenalin.

a. In rabbits.

A total of seventy-two injections of adrenalin was given to twenty-eight rabbits. The usual response was biphasic. There was an initial precipitous fall in potential followed by a rise in potential above the pre-injection value. The early part of the rise was rapid but later a decreased rate of increment occurred. After reaching a maximum value, the potential gradually returned to the original steady state potential level. The complete response lasted about five minutes. The time during which the potential was below the initial level occupied from a quarter to a fifth of the entire biphasic cycle. Figure II illustrates the typical response of the blood pressure and gastrograph records obtained with one milliliter doses of 1:4,000 to 1:40,000 adrenalin.

Some variations occurred, however, either in the blood pressure or in the electrical potential response following an injection of adrenalin. These changes may be grouped into two types; (i) those in which the blood pressure responses were not typical of adrenalin, while the potential did show a typical biphasic curve; (ii) those in which a typical blood pressure response was obtained but the electrical potential curves did not show the typical biphasic response. The former group will be illustrated first.

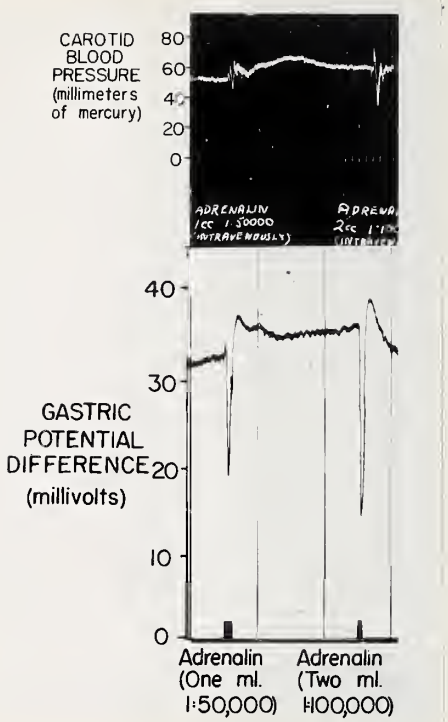

FIGURE III The effect of one milliliter 1:50,000 and two milliliters 1:100,000 adrenalin (7 ug. per Kg.) on carotid blood pressure and gastric potential difference. Rabbit 19.

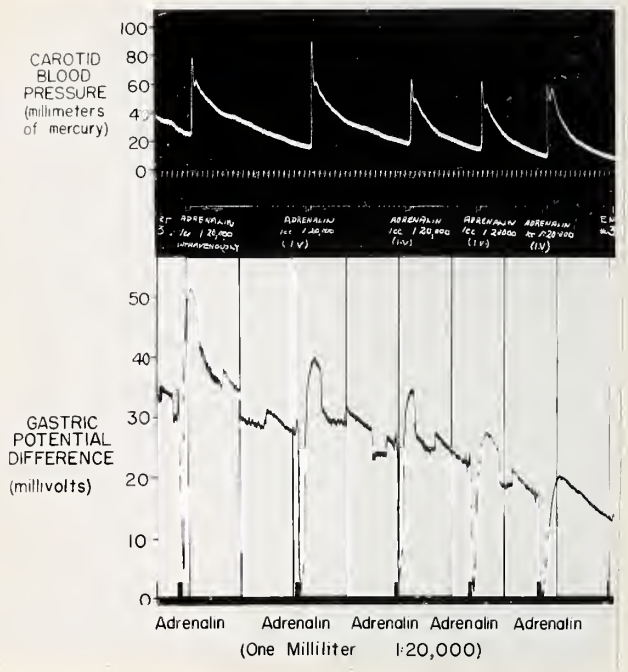

FIGURE IV The effect of repeated doses of one milliliter 1:20,000 adrenalin (13 ug. per Kg.) on progressively dropping blood pressure and gastric potential difference.

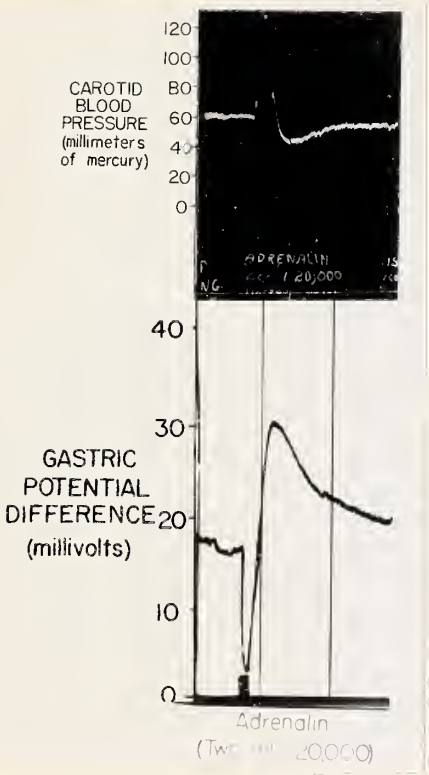

FIGURE Va
(12 ug. per Kg.)

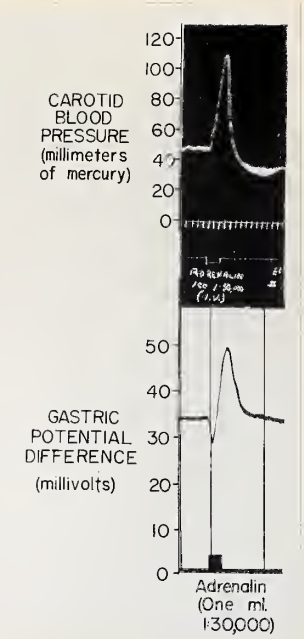

FIGURE Vb
(9 ug. per Kg.)

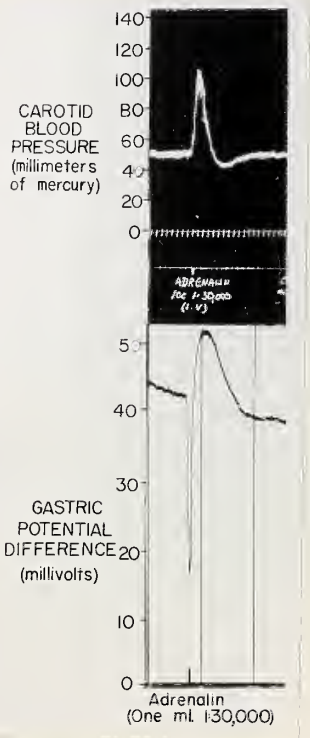

FIGURE Vd
(14 ug. per Kg.)

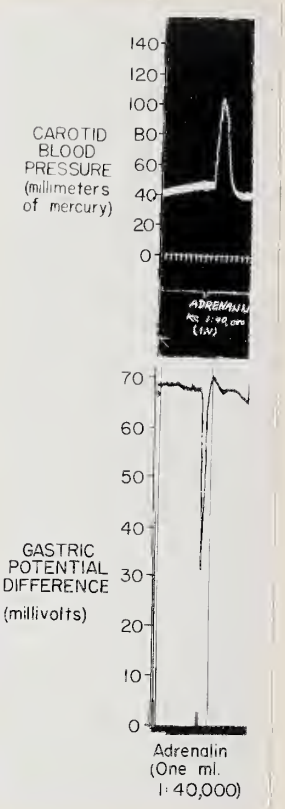

FIGURE Vc
(9 ug. per Kg.)

FIGURE V The effect of adrenalin on carotid blood pressure and gastric potential difference. Figures Va, Vb, Vc, Vd from Rabbits 6, 18, 16, 15 respectively.

(i) Injections of adrenalin smaller than one milliliter of 1:40,000 solution caused a biphasic potential difference response even though the peripheral blood pressure showed only slight change. (Figure III)

When in the course of an experiment the blood pressure shows a progressive drop, repeated injections of adrenalin cause typical biphasic potential changes, whereas the blood pressure shows only a pressor response followed by a gradual steady decline to a value below that present prior to each injection. (Figure IV)

A comparison of results illustrated in Figures II, III and IV indicates that although gastric potential changes are typically biphasic, the circulatory response can show a marked variation from the typical result following an injection of adrenalin.

(ii) The second group of observations comprises those in which the blood pressure response to adrenalin was typical, although variations in the characteristic biphasic electrogastrograph record occurred. This is illustrated in Figure V and shows the possible relationships existing between the magnitude of the decrease and the magnitude of the increase in potential difference.

In Figure Va the decrease and increase are of equal magnitude. In Figure Vb the decrease is only a small fraction of the increase, while in Figure Vc the converse is true. Figure Vd illustrates the typical response in which the magnitude of the decrease is about four or five times the magnitude of the increase.

In the total series of adrenalin injections, the decrease in potential varied from three to forty millivolts, while the increase ranged from one to twenty millivolts.

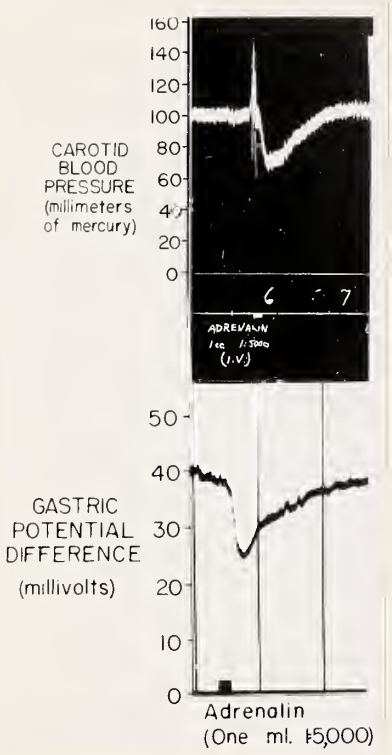

FIGURE VIa
(12.5 ug. per Kg.)

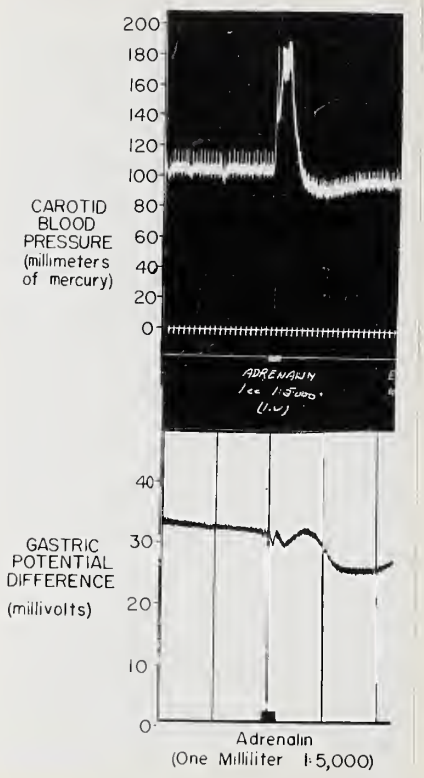

FIGURE VIb
(14 ug. per Kg.)

FIGURE VI The effect of one milliliter 1:5,000 adrenalin on carotid blood pressure and gastric potential difference. Figure VIa, Dog 43; Figure VIb, Dog 48.

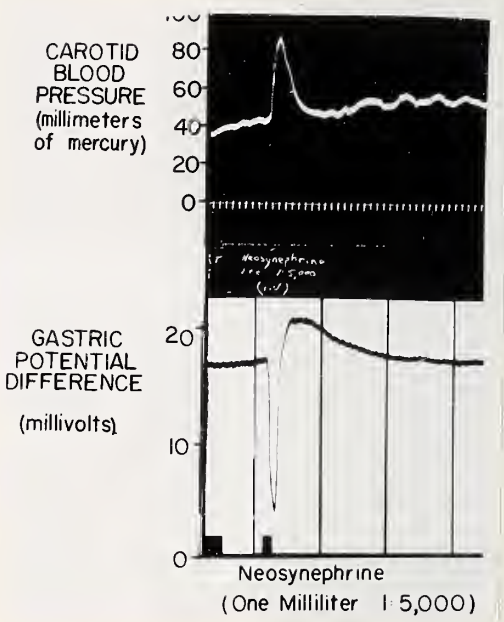

FIGURE VII The effect of one milliliter 1:5,000 neosynephrine (75 ug. per Kg.) on carotid blood pressure and gastric potential difference. Rabbit 25.

b. In dogs.

Rice and Ross (88) observed two types of responses to adrenalin in dogs. One was monophasic in nature, a fall in potential followed by a steady return to resting value. The other was called biphasic in nature. It consisted of an initial drop in potential, followed by an increase toward normal followed by a secondary drop. Occasionally the increases exceeded the resting value.

Fourteen injections of adrenalin (one milliliter 1:1,000) were given to seven dogs. All the responses but one (Figure VI) were of the monophasic type. The drop in potential usually did not exceed ten millivolts.

2. Neosynephrine.

It is evident that the potential changes due to neosynephrine (Figure VII) are similar to the usual response due to adrenalin. The blood pressure curves, however, show only an increase. A pressor response only is the normal pharmacological action of neosynephrine on blood pressure.

3. N-isopropylarterenol. #

Although classified as a sympathomimetic amine, this substance is said to cause a diffuse vasodilitation with a concomitant decrease in blood pressure (58). It was also found that the response of an animal to a particular dose might be quite variable. This fact was borne out by the observations which were made in this series of experiments.

Twenty-one injections produced a decrease in peripheral blood pressure in only seventeen instances. Of these, twelve showed an increase

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N-isopropylarterenol is marketed commercially as Isonorin by the Carroll Dunham Smith Pharmacal Company, New Brunswick,N.J. It is also known as Isuprel with the following structural formula: 1 - (3-4 dihydroxyphenyl) 2 isopropylaminoethanol - 1 sulphate.

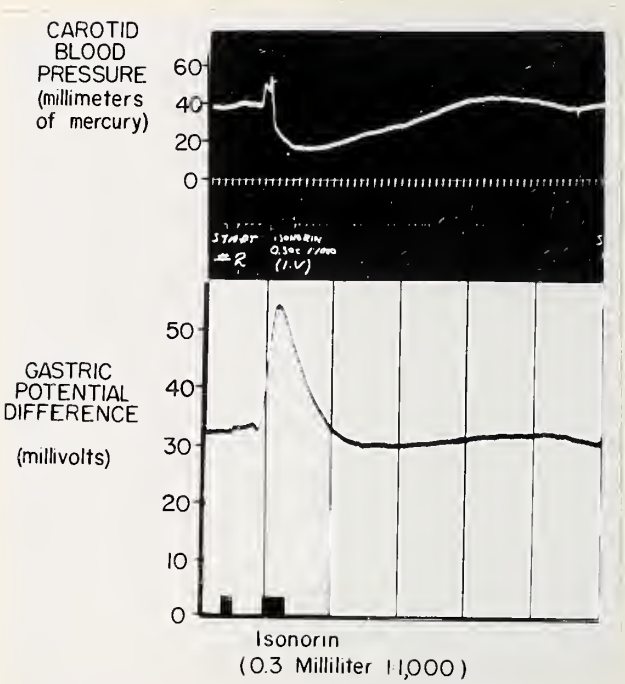

FIGURE VIII The effect of 0.3 milliliters 1:1,000 Isonorin (88 ug. per Kg.) on carotid blood pressure and gastric potential difference. Rabbit 18.

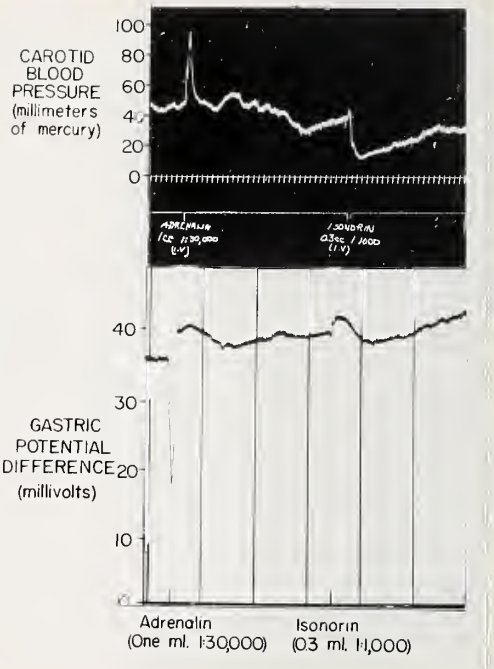

FIGURE IX The effect of one milliliter 1:30,000 adrenalin (14 ug. per Kg.) and 0.3 milliliters 1:1,000 Isonorin (140 ug. per Kg.) on carotid blood pressure and gastric potential difference. Rabbit 15.

in gastric potential difference. The results are particularly important in that they provide the first indication that an increase in potential might result from the administration of a pharmacological agent. It is worth emphasizing that this occurred with a substance which is described as a vascular dilator.

The increase in potential which occurred was from one to twenty-one millivolts. It was maintained from two to six minutes and was always of shorter duration than the change in blood pressure. (Figure VIII)

Rabbits which showed large increases in potential during the latter part of the biphasic adrenalin response also showed large increases in potential due to N-isopropylarterenol. A comparison of Figures Vb and VIII which were both made from tracings from Rabbit 18 illustrates this statement.

Conversely also, those rabbits which showed only a small increase in the positive phase of the changes which occurred due to adrenalin also showed only a slight increase in potential due to Isonorin. (Figure IX)

Of the nine Isonorin injections which did not cause an increase in potential difference, four caused decreases and five were equivocal. The blood pressure response to Isonorin, if it occurred, was always a sudden drop in pressure with a gradual return to previous levels in five to twenty minutes.

In summary, it may be stated that N-isopropylarterenol caused an increase in gastric potential difference in rabbits. The increase which occurred bore a definite relationship to the increase which occurred during the latter part of the biphasic potential response to adrenalin, when both drugs had been injected into the same rabbit.

4. Benzedrine sulphate.

Eleven doses of benzedrine sulphate were injected into five rabbits,

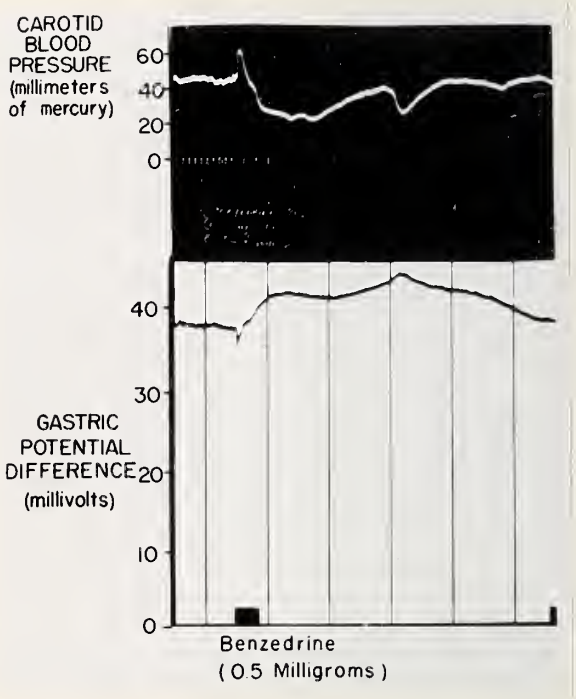

FIGURE X The effect of 0.5 milligrams of benzedrine sulphate (0.15 mg. per Kg.) on carotid blood pressure and gastric potential difference. Rabbit 32.

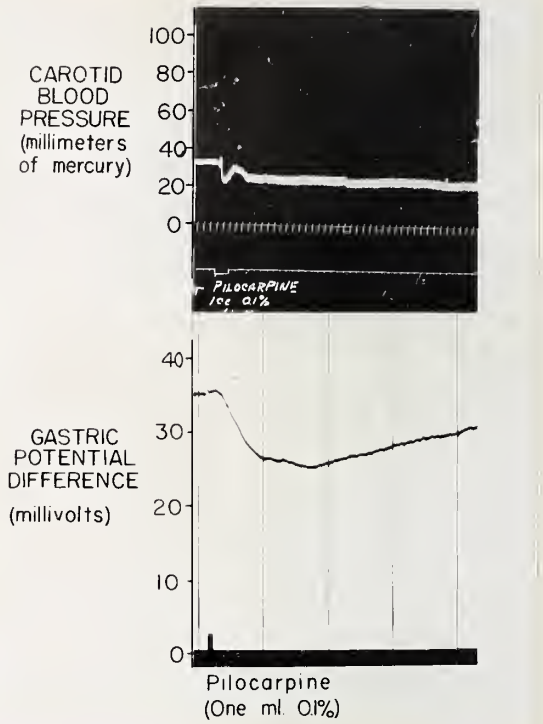

FIGURE XI The effect of one milliliter of 0.1% pilocarpine hydrochloride (0.35 mg. per Kg.) on carotid blood pressure and gastric potential difference. Rabbit 19.

one of which died immediately after the intravenous injection of five milligrams. Three of the injections caused no changes in the electrogastrograms or manometer tracings. The remaining injections of from 0.2 to 5 milligrams all gave increases in potential. There was a sudden increase almost to maximal value in fifteen to thirty seconds, and a gradual return to previously existing levels requiring five to twenty minutes. (Figure X)

A blood pressure response to benzedrine was either absent or a drop in peripheral pressure was found. The drop was very rapid, with the return requiring from two to fifteen minutes. The curves were usually irregular and showed undulations during the drop in pressure.

Contrary to the effect of adrenalin, neosynephrine and Isonorin, the duration of the potential difference response with benzedrine was usually longer than the blood pressure response.

C. The Effect of Other Pharmacological Agents on Gastric Potential Difference and Carotid Blood Pressure.

1. Pilocarpine.

Rehm (84) and Rice and Ross (88) obtained a decrease in gastric potential and an increase in gastric secretion in dogs following injections of pilocarpine. In this work, decreases in potential were also observed in rabbits in response to pilocarpine. In the three rabbits used, it was impossible to collect any gastric secretions so the effect of pilocarpine on the secretion of hydrochloric acid could not be correlated with the potential changes which occurred.

The potential changes which occurred in the rabbit (Figure XI) were almost identical to those which Rice and Ross (88) observed in dogs. The potential gradually decreased about fifteen millivolts and finally returned to the steady state value in about thirty minutes.

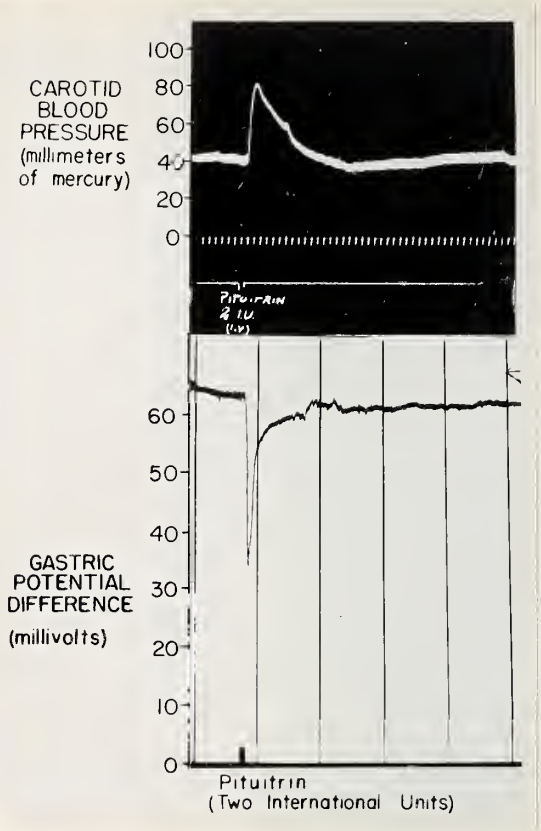

FIGURE XII The effect of two international units of pituitrin (0.75 I.U. per Kg.) on carotid blood pressure and gastric potential difference. Rabbit 16.

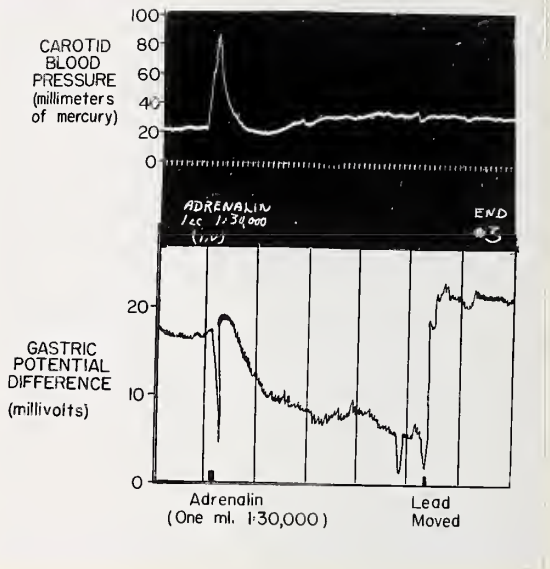

FIGURE XIII The effect on gastric potential difference of pressure exerted on the gastric musoca by the intragastric electrode. Rabbit 29.

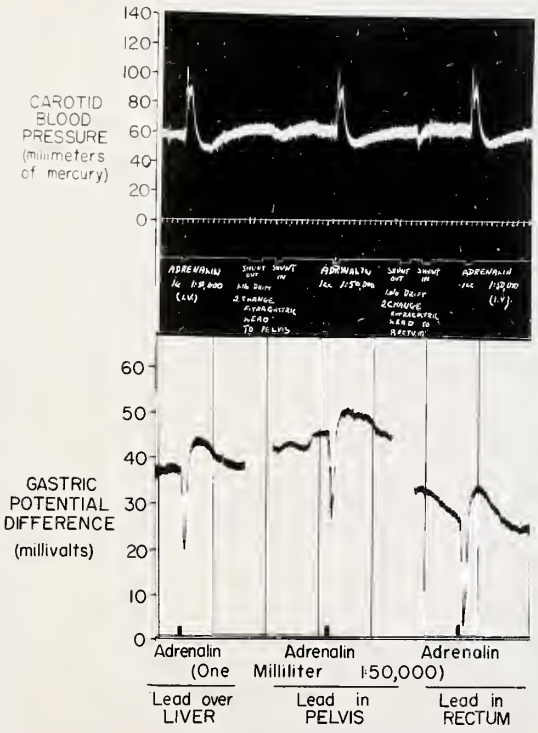

FIGURE XIVa

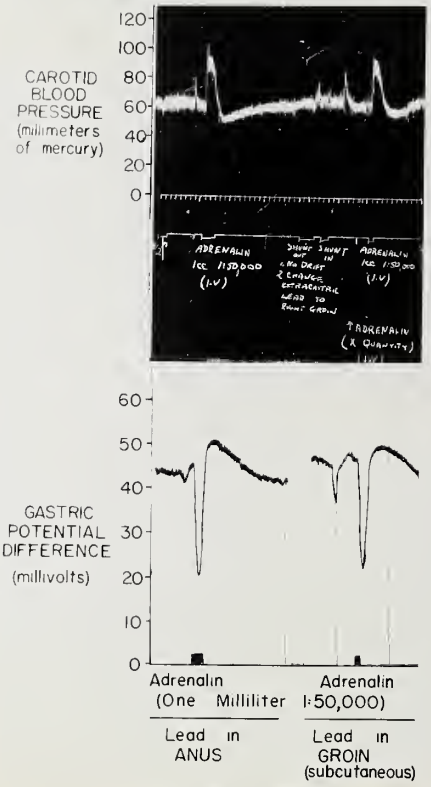

FIGURE XIVb

FIGURE XIV The effect on gastric potential difference of placing the extragastric lead in various areas of the body. Rabbit 35. Adrenalin, one milliliter 1:50,000 (6 ug. per Kg.)

The blood pressure was always decreased for the duration of the potential response.

2. Pituitrin.

Pituitrin caused a sudden drop in potential of about twenty-five millivolts. The potential then gradually increased within the next ten or fifteen minutes until the value of the resting potential was reached. (Figure XII). The blood pressure showed first an immediate increase of about twenty millimeters of mercury. The pressure then gradually decreased for the next ten minutes until it reached the previously existing level.

D. The Effect on Gastric Potential Difference of Pressure Exerted on the Gastric Mucosa by the Intragastric Electrode.

If any pressure were exerted by the intragastric electrode on the mucosal surface of the stomach, a gradual drop in potential occurred. When the pressure was released, (Figure XIII), the potential immediately increased to approximately pre-existing levels. The holes which had been cut in the intragastric lead prevented the electrode from becoming occluded when it was pressed against the gastric mucosa.

E. The Effect on Gastric Potential Difference of Placing the Extragastric Electrode in Various Sites.

Figure XIV illustrates the effect of placing the extragastric lead on the superior surface of the liver, in the pelvic area, in the rectum, anus and subcutaneous tissue of the right groin. The response of the potential difference to an injection of adrenalin was not significantly modified by the location of the extragastric electrode. However, the magnitude of the potential difference did change when the electrode was moved from one site to another. This is probably a reflection of the increased resistance of

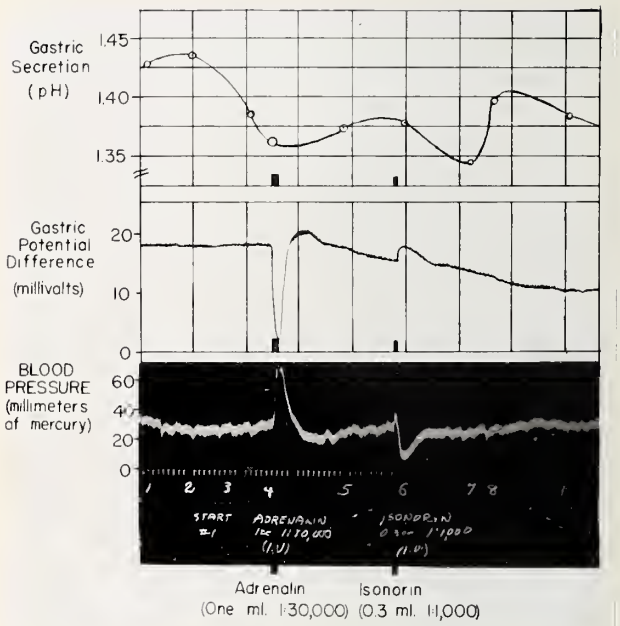

FIGURE XV Simultaneous records of the changes which occurred in the pH of gastric secretion, gastric potential difference and carotid blood pressure. Rabbit 21. One milliliter 1:30,000 adrenalin (11.5 ug. per Kg.); 0.3 milliliters 1:1,000 Isonorin (350 ug. per Kg.)

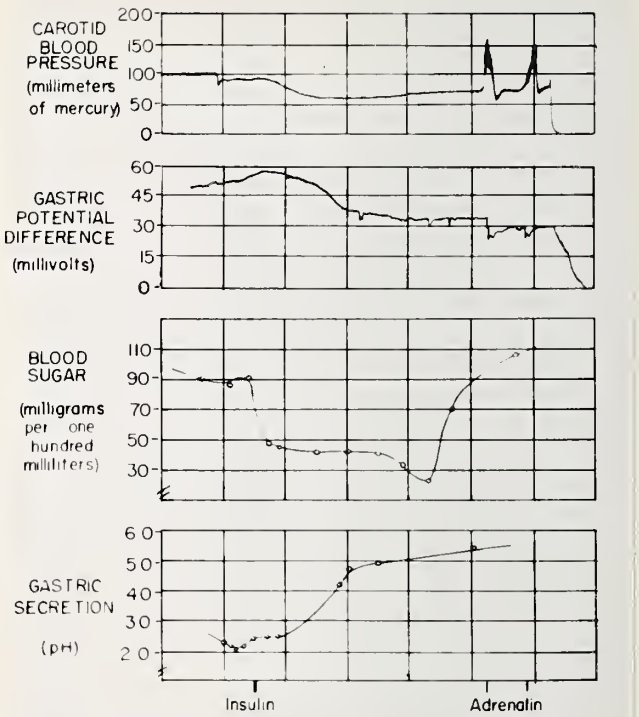

FIGURE XVI A scale drawing of the simultaneous carotid blood pressure, gastric potential difference, blood sugar and pH of gastric secretory changes which occurred in a dog during a seven hour period. Dog 47. Ten units of insulin (1.4 units per Kg.)

the intervening tissue. It is minimized by the use of a high resistance input recording system (88).

F. The Relationship between Gastric Secretion and Potential Following the Injection of:

1. Sympathomimetic agents and pituitrin.

In only seven of the rabbits used in these experiments was it possible to collect samples of gastric secretion while potential difference and blood pressure were being recorded. A record from one of these rabbits is illustrated in Figure XV. In comparing the gastric pH changes with the potential difference records, it becomes evident that there is no consistent relationship between the secretory response and the potential changes which occurred.

2. Insulin.

An attempt was made to stimulate gastric secretion in rabbits by producing vagal stimulation through insulin-induced hypoglycemia. The attempt was futile, however, since it was impossible to lower the blood sugar level sufficiently to produce vagal stimulation.

A similar attempt to stimulate gastric secretion by vagal stimulation in the dog was just as disappointing. In this animal, with a slight modification of technique from that used in the rabbit work, hypoglycemia sufficient to produce vagal stimulation was obtained. However, there was no corresponding increase in gastric secretion once the blood sugar level was low enough to cause vagal stimulation.

A scale drawing of the simultaneous blood pressure, potential difference, blood sugar and gastric secretory changes which occurred in a dog during a seven hour period is illustrated in Figure XVI. The vertical lines

in this illustration are drawn at intervals of one hour. Following the injection of insulin, the blood sugar fell from ninety to less than fifty milligrams per one hundred milliliters. However, there was no apparent increase in the volume of gastric secretion which would be expected to have occurred following the central vagal stimulation due to hypoglycemia. It does appear, however, that the rate of mucoid and peptic secretion exceeded the rate of secretion of hydrochloric acid since there was an increase in gastric pH. The gastric potential, however, decreased following the injection of the insulin and unless it occurred spontaneously, would possibly suggest that there had been a stimulation of acid secretion. But as pointed out previously, this did not occur. In this animal the duodenum was ligatured so there was little possibility that acid secretion occurred which was not collected.

G. Miscellanea.

A few injections of priscoline were given to several rabbits and dogs, but the results did not show any particular trend. The number of observations was too small to allow any conclusions to be made. A few observations in dogs following injections of N-isopropylarterenol suggest that a drop in potential occurs and not a rise, as is found in the rabbit. As in the case of priscoline, more observations are required before conclusions can be made.

The effect of hemorrhage and the intravenous injection of forty milliliters of hot (45°C.) and cold (4°C.) 0.9% saline solutions on electrical potential did not provide significant results. Since these procedures produced gross changes in the physiological state of the animal, subsequent records which could be compared with previous records were not obtainable. Consequently, no attempt was made to obtain sufficient data for analysis. The effect of these two procedures on potential difference in relation to

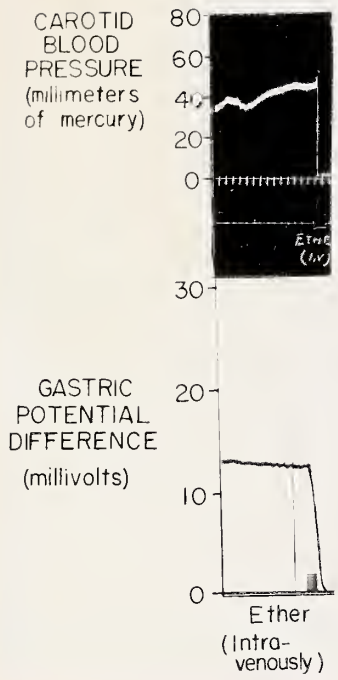

FIGURE XVIIa
Rabbit 25.

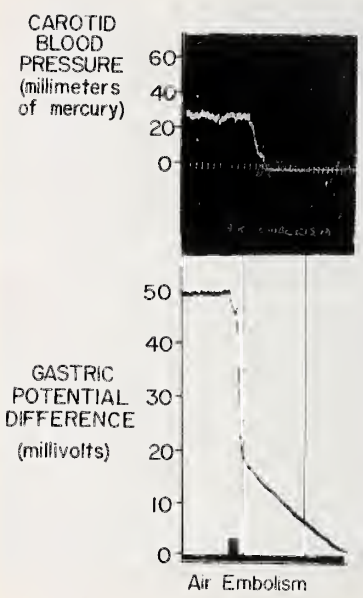

FIGURE XVIIb
Rabbit 19.

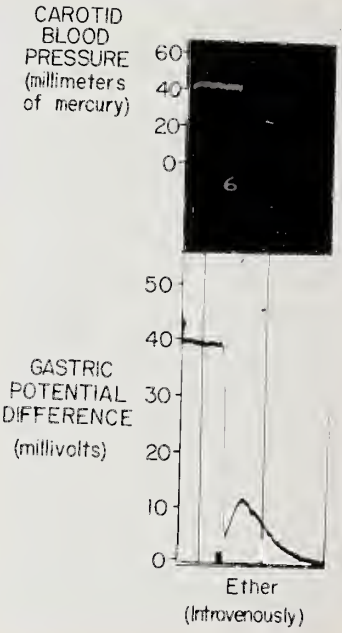

FIGURE XVIIc
Rabbit 29.

FIGURE XVII The effect of death on carotid blood pressure and gastric potential difference.

circulatory adjustments are perhaps deserving of future investigation.

H. The Effect of Death on Gastric Potential Difference and Carotid Blood Pressure.

1. In rabbits.

A record was made in twenty-six rabbits of the potential and blood pressure changes which occurred at death. In some instances death occurred spontaneously, perhaps from an overdosage of anesthetic, or else death was purposely caused by an injection of air, ether or chloroform into the femoral vein.

In all the rabbits, the blood pressure quickly dropped to zero. The potential difference change, however, was not as uniform as the blood pressure response. In fifteen cases, the potential difference also dropped suddenly. The dropmusually required only a matter of seconds to be completed. (Figure XVIIa). In Rabbit 19, however, after an initial precipitous fall in potential, the decrease was more gradual and the potential reached the base line in ten minutes. (Figure XVIIb). This type of curve is similar to that occurring in dogs at death (85).

In eleven rabbits, an initial sudden decrease in potential occurred but then the potential began to rise and finally decreased. This secondary rise never attained the steady state level. The time required for the complete response in these animals was quite variable. The longest required about two hours to return to the potential base line, while the shortest required only about five minutes. This type of response is illustrated in Figure XVIIc.

2. In dogs.

The effect of death on potential was followed in the eleven dogs used in these experiments. In four animals the cause of death was undetermined;

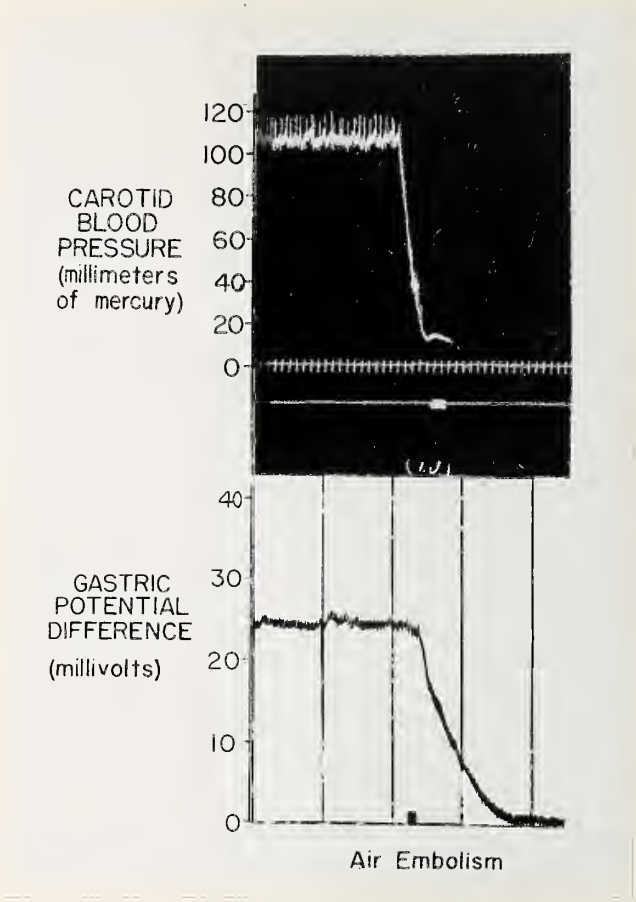

FIGURE XVIII The effect of death on carotid blood pressure and gastric potential difference. Dog 47.

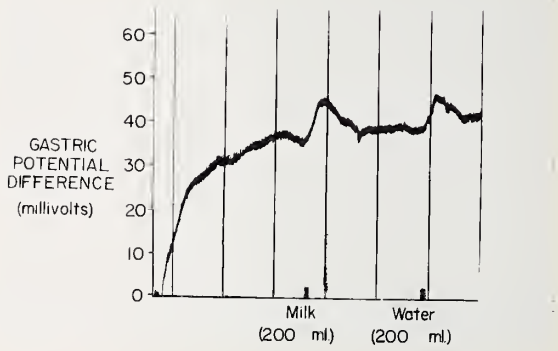

FIGURE XIX The effect on humans of the oral ingestion of two hundred milliliters of milk and two hundred milliliters of water on gastric potential difference.

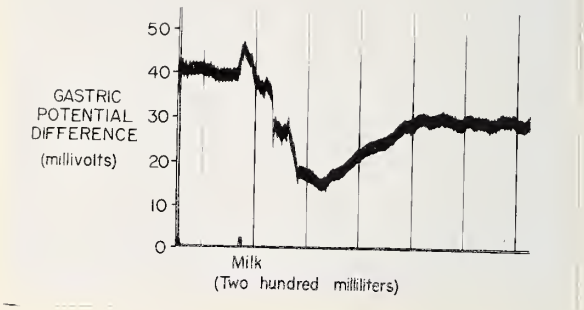

FIGURE XXa

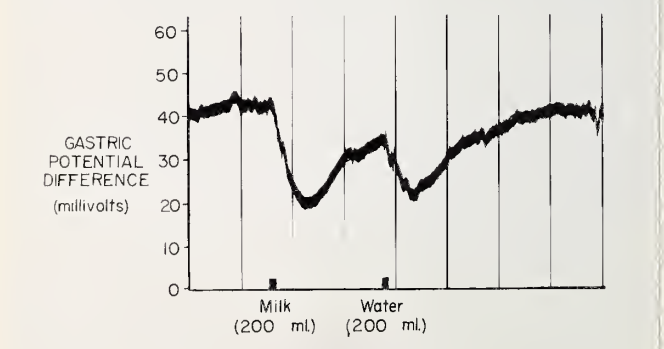

FIGURE XXb

FIGURE XX The effect on human beings of the oral ingestion of two hundred milliliters of milk and two hundred milliliters of water.

in four, death followed the intravenous injection of chloroform, and in the other three, death followed either the intravenous injection of sodium pentothal, sodium amytal or Isonorin. In all cases the drop in potential difference occurred in the same way. (Figure XVIII). An initial decrease to about half the pre-existing level occurred suddenly. In the following ten or fifteen minutes, the drop in potential was more gradual until no potential difference was recorded. These results were similar to those reported by Rice and Ross (88).

I. The Measurement of Gastric Potential Difference in Humans.

A series of nineteen experiments was conducted in which the effect of the oral ingestion of milk on gastric potential in humans was recorded. Contrary to the observations of Quigley et al (70), the usual response was a drop in potential rather than an increase in potential difference.

Only two increases in potential difference were recorded. One of these is illustrated in Figure XIX. The time required for the increase to occur was of about the same duration as the time required for the potential to return to the resting level. In both instances, the potential was raised above the resting level for approximately five minutes. In Figure XIX the increase in potential was about ten millivolts. In this subject, the response of the potential to the ingestion of water was the same as the response to the ingestion of milk.

In the other seventeen records, the ingestion of milk produced a decrease in potential. Both the extent and duration of decrease varied over a fairly wide range. The potential dropped ten to twenty-five millivolts and returned to near the steady state level in from fifteen to thirty minutes. (Figure XX)

In those subjects in whom time permitted, a drink of water was given after the milk. The response was similar to that with milk, but usually of less magnitude and of shorter duration. The response to both milk and water is illustrated in Figure XXb.

SECTION VI

DISCUSSION AND CONCLUSIONS

Section VI.

Discussion and Conclusions.

A. The Steady State Potential.

The increases in potential illustrated in Figures I and XIX are possibly the result of cessation of reflexes due to operative procedures in animals or psychic influences in human subjects. This observation is of importance when working with animals since sufficient time must be allowed for this increase to occur, and for the steady state potential to become stabilized before any experimental changes in potential are initiated. In dealing with human subjects, however, the increases which appear to be the result of emotional disturbances are dependent upon more subtle and obscure influences. As a result, care should be taken to make the subject comfortable and to minimize extraneous stimuli. After suitable precautions have been taken, it is then necessary to wait until a steady state potential has been reached and maintained for several minutes before any test changes are induced. Even at this time it has to be assumed that reflex influences are minimal and that the subject will be responding only to the tests which are employed.

The low values of the steady state potential which were recorded in the first thirteen rabbits were probably due to at least two causes. Firstly, the preparation and intra-abdominal manipulation which was required to tie the esophageal and cardiac ligatures, remove some of the gastric contents, and tie the glass tube into the stomach, resulted in considerable trauma. Other investigators (23, 88) have found that excessive handling of the gastric mucosa results in low steady state potentials being recorded. Secondly, the coarse food fed to these thirteen rabbits caused a very thick coating of

viscous mucous to be secreted over the mucosa of the stomach. It was only after this covering was removed that the usual pink color of the mucosa was visible. It is possible that the presence of this coating was also in some was responsible for the low values of potential recorded.

After eliminating the operative procedures and obtaining a suitable intragastric medium by controlling the diet of the remaining twenty-seven rabbits, the gastric potential differences which were recorded were usually higher than those recorded in the first thirteen rabbits. Since both the procedure and diet were changed at the same time, it is impossible to state which of these factors was primarily responsible for the low potentials recorded in the first series of rabbits. It should be pointed out, however, that there was no significant difference in the results when changes were induced in the electrical state in rabbits with a low or a high steady state potential.

In the dogs used, the average potential recorded was comparable to the average value found by Rehm (72).

B. Circulatory Changes and Gastric Potential Difference.

The conclusion can be reached that the electrogastrograph reflects changes in oxygen transport to the gastric mucosa, a decrease in oxygen supply as from vasoconstriction (88), prolonged fall of blood pressure (61, 83), mechanical interference with blood flow (9, 76), circulatory failure (21, 94), anoxia (84), etc., will cause a fall of gastric potential, whereas increased oxygen transport to the mucosa as from dilator drugs, the hyperemic phase of the adrenalin response or the elimination of constrictor influences, etc., cause a rise of potential. The significance of these two observations would appear to be that the transient changes of the gastric electrical potential

may be of use as an index of circulatory changes occurring in the stomach.

The discussion of some of the results obtained in these experiments will be resolved into several points for consideration.

1. At the present time it is impossible to arrive at a conclusion concerning the circulatory changes that will occur in the gastrointestinal tract from any procedure which modifies the blood pressure especially through generalized vasomotor adjustments. But it does appear from these experiments that where one can be relatively sure of splanchnic vasoconstriction the potential falls, or of splanchnic vasodilatation the potential increases. If such a correlation can be proven by more specific observations on splanchnic blood supply, the use of the electrogastrograph as a clinical means of assessing gastric circulation would be established. It must be admitted that such a final conclusion can not be reached from these experiments in which correlations only between carotid blood pressure and gastric potential have been made.

2. A difficult aspect of the problem to be explained is the fact that a great variability of circulatory response occurs in different species when blood pressure changes are used as the criterion of vascular adjustment. It would appear, for example, that under the influence of adrenalin the dog shows a predominant vasoconstrictor reaction. But nevertheless one must consider that compensatory dilitation may occur which is not clearly evident from blood pressure records. The rabbit, however, appears to show an initial vasoconstrictor response and a subsequent dilator response. A comparison of the dog and the rabbit both from the literature and these results suggests that much more marked intestinal vascular changes occur in the rabbit than in the dog. It has also been demonstrated in these experiments that more marked changes in electrical potential occur in the rabbit than in the dog.

3. At the same time it is also true that a great variability can occur between different animals of the same species in circulatory adjustments in the periphery and splanchnic areas, and in gastric potential differences under the influence of drugs which affect the circulation.

4. In any given animal, however, the pattern of response to a particular procedure is consistent both in regard to circulatory changes and potential changes.

To reiterate, although it is impossible to arrive at a conclusion concerning the circulatory changes that occur in the gastrointestinal tract from any procedure which modifies the blood pressure through generalized vasomotor adjustments, it appears that splanchnic vasoconstriction is associated with a decrease in gastric potential and splanchnic vasodilatation with an increase in potential. In the light of the detailed arguments presented below such a correlation seems probable.

1. Adrenalin, Figures II, III, IV, V, VI; neosynephrine, Figure VII; N-isopropylarterenol, Figures VIII, IX and XIII; benzedrine sulphate, Figure X, and pituitrin, Figure XII, all cause changes in carotid blood pressure and gastric potential difference. The duration of the potential changes which occur is of approximately the same duration as the vascular responses which occur. In general those substances which are pressor in nature cause a decrease in potential and those which produce a drop in blood pressure result in an increase in potential. Adrenalin, neosynephrine and pituitrin, which are potent pressor agents, cause a decrease in gastric potential. The sympathomimetic agent N-isopropylarterenol causes a decrease in carotid blood pressure and an increase in potential. Benzedrine does not consistently produce a potential change, but when a change in potential does occur, it is always an increase. The intestinal circulation in many instances shows an

inverse relationship to peripheral circulatory changes. If this is the case, those agents which cause an increase in intestinal and consequently gastric circulation would be associated with an increase in gastric potential. Although this generalized statement appears in the light of available evidence to be true, still more detailed examination of the intimate relationship between potential and circulation in the stomach is required to prove the detailed relationship.

Another significant observation which incriminates the circulatory system as being active in producing some of the potential changes which occur in the stomach was obtained through personal communication with Rice (88). The reversal of the adrenalin response which occurs following ergotoxin administration is also associated with almost complete elimination of the usual change in potential following adrenalin. Occasionally a slight decrease in potential occurs during the time in which the blood pressure has dropped. These results are further evidence that the potential changes due to adrenalin are of vascular origin.

2. The response to adrenalin in the dog (Figure VI) and the rabbit (Figures II, III, IV, V) of the gastric potential shows a marked variation between these species. The response, however, appears to follow the course of the intestinal vascular changes which occur. The decrease in potential is apparently the result of intestinal vasoconstriction and the subsequent increase in potential due to vasodilatation and increase in intestinal circulation.

The intestinal vasoconstriction due to adrenalin is a well accepted phenomena but the subsequent increase in volume as pointed out previously, (Section III) can result from several causes. This is interpreted by the author to account for the different effects observed in the dog and in the

rabbit. In the latter animal the increase appears to be the result of a mechanism which causes an increase in intestinal volume and also an increased blood flow which increases the oxygen carriage to the mucosa. This results in the potential being raised above the steady state potential for a short time following the initial constrictor phase. In the dog, however, the effect appears to be one in which the increase in volume is associated with very little increase in blood flow. As a result, in the dog there is no secondary rise of potential above the steady state value following a dose of adrenalin, and the return of the potential to the initial values would appear to occur only as oxygen transport to the tissues or the initial circulatory state is restored.

As previously stated (Section III) large doses of adrenalin at first decrease intestinal volume and later cause an increase to occur. However, volume changes in an organ are not indicative of the volume flow occurring in that site. Until simultaneous records of gastric blood flow and gastric potential changes are made, the interpretation of the electrogastrographic record must of necessity be speculative or theoretical.

If a strict correlation between blood flow and potential changes can be proven, an important step will have been made toward obtaining a means of assessing intestinal circulation. A simple technique would then be available which would make possible observations which previously have been difficult, open to considerable experimental error and indeed usually impossible.

3. It has been noted that the blood pressure and gastric potential responses due to a particular agent do not always follow similar patterns.

A comparison of results illustrated in Figures II, III and IV indicates that although gastric potential changes are typically biphasic, the circulatory response can show a marked variation from the usual result follow-

ing an injection of adrenalin. The response to Isonorin (Figures VIII & IX) also illustrates this point. The conclusion to be drawn from such observations can only be that the peripheral vascular responses as indicated by carotid blood pressures are not a good measure of the intestinal vascular response. To obtain a detailed knowledge of changes in the stomach requires a procedure permitting direct measurement of blood flow to be made in this organ.

To emphasize further the variability in different animals which exists between peripheral and intestinal circulatory adjustments the changes which occurred due to adrenalin illustrated in Figure V are discussed.

It can be seen that although the carotid blood pressure curves are similar the potential changes are quite variable. If the potential changes due to adrenalin are dependent on vascular phenomena the results suggest that the effects of adrenalin are mediated to the intestinal circulation in a somewhat unpredictable manner. The predominant change which occurs in potential difference can be either a decrease or increase. An inspection of the blood pressure record does not indicate which occurs and consequently blood pressure can be said to be a poor indicator of the finer vascular adjustments which occur in the intestinal circulation. Again if the finer correlations between potential changes and adjustments of blood flow in the stomach are proven the electrogastrograph could be used as an index of the circulatory state in this organ.

4. The last point relating circulatory adjustments and gastric potential to be emphasized is that in any particular animal the potential response to a particular agent is predictable and can be reproduced. This observation is illustrated in Figure III in which two subsequent injections of adrenalin are given. In both instances the potential responses are similar. The consistency of response in an animal can be carried further to include

the response to different agents. For example, when a marked increase in potential in the latter part of the biphasic cycle due to adrenalin occurred (Figure Vb) the response of N-isopropylarterenol was also great (Figure VII). However, when only small increases in potential with adrenalin occurred, only small increases in potential due to N-isopropylarterenol were found (Figures IX and XV). As a result it is concluded that the intestinal vascular re-adjustment due to circulatory changes do not vary greatly in any particular animal.

Thus it would appear that a marked vasoconstrictor tendency from any cause in a particular individual is reflected in a marked tendency toward a lowering of gastric potential, and conversely, a marked vasodilator tendency from any cause is associated with a great increase in gastric potential.

C. Gastric Secretory Activity and Gastric Potential Difference.

The review of the literature presented previously reveals that the majority of reports dealing with gastric potentials have been concerned mainly with the relationship between secretion and potential difference. Thus it has been shown that the active stimulation of gastric secretion by histamine, (23, 72, 74), pilocarpine (74, 88) and mecholyl (84) is associated with a reduction of potential, and the cessation of secretion as from neutralization by atropine (84, 88) or the simple dissipation of the stimulant agent is associated with the return of the gastric potential to the steady state value.

These potential changes due to active secretion have two important aspects. First, they are apparently of long duration, lasting as long as the secretion of acid occurs. This is in marked contrast to the majority of changes in potential which result from vasomotor changes such as a startle or a dose of adrenalin. These latter changes last only a few minutes. In the

majority of instances therefore, changes in electrical potential from secretory stimulation can be differentiated from changes in potential which occur due to circulatory adjustments. But while in general therefore the two types of potential change can be differentiated, such differentiation is not always possible. For example, under circumstances where prolonged reflex or other vasoconstriction is present, a prolonged fall of potential will also exist which could not be differentiated from a.low potential due to maintained gastric secretion. This point is to be emphasized because it introduces a most importanc complicating factor in the interpretation of the human electrogastrogram. A patient, for example, under emotional stress, or showing anxiety, or in whom the simple passage of the tube evokes considerable discomfort, the potentials may be low due to the resulting circulatory response. On the other hand, a similarly low potential record may result from gastric secretion even in the absence of a primary sympathetic response. It is one purpose of this thesis to point out, therefore, that the simple interpretation of the electrogastrogram as a measure of gastric secretory activity is open to criticism.

The second point is that whereas potential changes resulting from active secretion are always in the nature of a drop below the steady state potential, vasomotor adjustments if they involve a dilator component may be associated with a rise of potential above the steady state value.

The relationship between vasomotor adjustments and potential difference has been dealt with in detail partly because it appears that it may be necessary to recognize in the future that the differentiation between secretory potential decreases and vasomotor potential changes may depend upon the ability to restore the latter to normal by invoking a vasodilator reaction. This offers a possible means of clarifying the complication dealt with in

the previous paragraph.

From the results obtained in these experiments it does not appear that the transient potential changes which have been attributed to circulatory adjustments have any relationship to gastric secretory activity. Figure XV is an illustration of the changes which occurred in the pH of the gastric secretion, potential difference and blood pressure. It is evident that there are no changes in gastric pH comparable to those occurring in potential difference due to adrenalin or Isonorin (N-isopropylarterenol).

It should be pointed out, however, that there are inherent difficulties in attempting to evaluate the results illustrated in Figure XV. The only indication that gastric secretory changes are occurring was obtained from the pH determinations. Among the many factors which affect the value of gastric pH besides the secretion of acid are the secretion of mucoid and peptic substances and duodenal regurgitation (95, 96, 98). High pH values and greenish coloration of the samples which were collected indicated that duodenal regurgitation had occurred. However, the diluting and acid neutralizing effects of the mucoid and peptic substances on gastric pH could not be assessed. Another difficulty encountered in the attempt to relate secretory, potential and vascular changes was that the short duration of the vascular responses did not allow more than one or two samples of secretion to be collected while the changes were occurring. Only if continuous or nearly continuous pH recording were used could the secretory response be adequately compared with the vascular and potential responses.

In summary it may be stated that although the evidence is not conclusive, it does appear that the transient potential changes which occur concomitantly with circulatory adjustments are not the result of secretory activity in the stomach.

The effects of pilocarpine and insulin on gastric secretion were also investigated. Pilocarpine has an effect on potential difference of the rabbit which is almost identical to the effect observed in dogs (88).

Previous investigators have been unsuccessful in recording the potential changes due to secretion which occurs during electrical stimulation of the vagus (61, 84, 88). Insulin was used in these experiments to produce vagal stimulation since it eliminates many of the difficulties encountered when the vagus is stimulated electrically. The low blood sugar due to insulin stimulates the vagus center in the brain and produces a secretion of typical vagal juice (3, 41). Section of the vagi or large doses of atropine stop the secretion of acid following insulin. These observations were used as evidence for the assumption that the stimulation was central in origin (4).

In the rabbits used in these experiments, it was at first impossible to lower the blood sugar level sufficiently with insulin (below sixty milligrams per one hundred milliliters) to produce central vagal stimulation. The failure occurred since the hyperglycemia due to the ether (59, 89) which was used as the anesthetic could not be changed to hypoglycemia with insulin.

When sodium amytal which does not cause hyperglycemia (19, 46, 68) was used as the anesthetic, it was possible to produce vagal stimulation. However, the difficulty encountered in obtaining samples of gastric secretion from the rabbits did not allow any correlation between gastric pH, potential difference and blood sugar levels to be made. The results of the injection of insulin into the eleven dogs used in these experiments were equivocal. An examination of results illustrated in Figure XVI shows that as the blood sugar level decreased a drop in potential occurred. This is what would be expected. The vagal stimulation due to the effects of insulin would cause the secretion of acid and consequently a drop in potential difference. Vagal

stimulation produces a gastric secretion of high acidity, good peptic activity and rich in mucus. It is possible therefore that the acid which was secreted was neutralized and diluted by the peptic and mucoid substances so that an increase in pH occurred even though a strongly acid secretion was stimulated. However, there was no increase in the volume of secretion which would also have been expected to occur with prolonged vagal stimulation. This experiment is typical of the results which were obtained from the other dogs in that some necessary results were required before conclusions could be made. It is suggested that the effect of vagal stimulation be repeated using a technique which permits an accurate collection and a greater variety of determinations to be made on the gastric secretions.

D. Placement of the Electrodes.

1. The intragastric electrode.

The fundus has a higher potential difference than the pylorus (23, 88). Consequently it is important to know the location of the electrode when an interpretation of the steady state gastric potential is being made. In human beings the difficulty of determining the location of the electrode can be overcome by making a roentgenogram since the electrode used in these experiments contains metals which would be visible on X-ray examination.

2. The extragastric electrode.

The location of the extragastric lead has little effect on the record as long as it is not placed on an area which itself has a large potential difference. For example, only a few millivolts change is recorded in potential difference when the lead is placed over the liver, in the pelvic area or in the subcutaneous tissues. (Figure XIV). However, a marked difference occurs when the lead is placed in the rectum or anus. This is due to the opposing effect of the potential difference found in the rectum, which

is frequently as high as twenty-five millivolts (23). The anus, although not possessing a significant potential difference, is a difficult site in which to fasten the electrode, which can easily slip into the rectum and record spurious potentials.

In the human beings on whom electrogastrograms were made, the electrode was placed on the antero-lateral surface of the lower third of the upper arm. This area has as few sweat glands as any area of the body (56) so it was thought that potential difference of the secretory glands in this site would be as low as any found on the body surface.

E. Death and Gastric Potential Difference.

Clinical death in the dog and the rabbit is associated with a decrease in gastric potential to zero (Figures XVII, XVIII). In the dog, (Figure XVIII), the potential usually falls suddenly for a short time and then gradually falls until no potential difference is recorded between the two electrodes. In the rabbit (Figure XVII), the drop in potential occurs in several ways. The different types of response are possibly due to diffusion potentials. However, until more evidence and knowledge of gastric potential changes, secretory and metabolic activity is gained, the differences in the type of response found does not seem to justify further comment.

F. Potential Changes in Humans.

A few investigators have attempted to make the electrogastrograph of use in the diagrams of gastric lesions (31, 70, 94). The potential changes in response to the ingestion of milk have been used as the basis for the diagrams. However, even in the so-called normal humans on whom gastric potential difference changes were recorded in these experiments, a wide variation of response occurred following the ingestion of milk. The usual response, contrary

to other observations (31, 94) was found to be a decrease in potential difference. Both the magnitude and the duration of the decrease varied over a wide range. The potential response even varied from day to day in the same subject. Another finding was that the response to a drink of water was almost identical to the response to milk, when both could be given to the same subject during one recording.

The limited number of observations made on human beings does not allow conclusions to be drawn, but nevertheless the results are suggestive evidence for the discussion which follows.

The usual decrease in potential which was observed following either the ingestion of milk or water was probably due to stimulation of acid secretion which, as pointed out previously (page 18), is associated with a decrease in gastric potential difference. Although no collection of gastric contents was made, it is probable that gastric secretion did occur. Ivy (40), for instance, has shown that the drinking of water stimulated the secretion of acid from the stomach. He also showed that four hundred milliliters of cool tap water was removed from the empty stomach in fifteen to thirty minutes. This corresponds closely to the duration of the gastric potential response also. As a result of these correlations, it is suggested that the secretion of acid caused the decrease in gastric potential to occur. Ivy (40) also pointed out that there was a great variability in the time required for emptying the stomach or in the amount of acid which was secreted. The variability of the response appeared to be partly dependent on such factors as the stimulation of psychic secretion, thirst, hunger, and the temperature of the room in which the test was done. He noted that in some subjects, no stimulation of secretion occurred. It is possible, therefore, that in the two subjects in whom an increase in potential was recorded, no secretion of acid occurred.

The increases could possibly have been the result of diffusion potentials which can occur between solutions of milk, water and saline (page 11).

As a result of the many variable factors which can influence gastric potential difference following the ingestion of milk, the writer does not believe that the milk response would be a suitable test when the electrogastrograph is to be used in the diagnosis of gastric lesions.

However, tests in which psychic influences are minimal might be able to be devised in which either the secretory and gastrographic changes could be correlated, or vascular adjustments and potential differences could be correlated. In humans if potential changes due to only one factor were known to be active, a susceptibility to hypersecretion or overactivity of the parietal cells could possibly be predicted on the one hand, or a predisposition to hypertension or other vascular derangements might be postulated. The reason for these statements being made is that the potential changes appear to be a more specific indication of cellular secretory activity than the overt changes in pH which may or may not occur following secretory stimulation (88), or else finer vascular adjustments are often recorded on electrogastrograms when there is little indication that such changes are occurring when measurements of blood pressure are made (page 42.).

Further investigation seems desirable since a useful field of diagnosis can possibly be opened, in the measurement of gastric potential difference.

SUMMARY

Summary.

1. A review and evaluation of some of the literature on gastric potential difference was presented.

2. Procedures and apparatus for recording the electrical potentials of the stomachs of rabbits, dogs and humans was described.

3. The results of a limited number of experiments on rabbits, dogs and humans were presented.

4. The significance and possible explanation of some of the results which were obtained was discussed.

5. The possible value of the electrogastrograph as a diagnostic aid was considered.

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